REMARKS

Authorization is provided to charge the fee for the extension of time and any fees that may be due in connection with the filing of this paper or with this application to Deposit Account No. 02-1818. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A Change of Address form accompanies this response.

Claims 1, 2, 5, 6, 10, 15, 17, 18, 22, 25, 34, 38, 41 44, 46, 47, 55, 56, 63, 66-68, 75, 77, 110, 116, 137, 139, 140, 143-147, 151-153, 155-158, 160, 161, 163, 164, 166-169, 171, 172 and 174 are pending. Claims 81,118, 120, 150 and 173 are cancelled without prejudice or disclaimer. Claims 81, 118 and 120 are directed to non-elected subject matter. Claim 157 is duplicative of claim 1. Applicant reserves to the right to file divisional/continuation applications to the subject matter of any cancelled claims or subject matter disclosed in the application. Claim 174, which finds basis in claim 81, is added.

Claims 5, 17, 18, 22, 44, 46, 47, 55, 56, 63, 66, 67, 68, 77, 143, 145, 146, 147, 153, 155, 156, 167, 168, 171, and 172 are indicated as withdrawn from further consideration by The Examiner indicates that claims 1, 2, 5, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160, 161, 163, 164, 166, 169 and 173 read on the elected species. The withdrawn claims are retained pending allowance of a generic claim. Claims 1, 10, 158, 159, 163 and 164 are amended for clarity. Claim 1 is amended to render it clear that X is activated to effect covalent binding to permit Y to reach equilibrium before capture. Claims 158 and 159 are amended to properly depend from claim 1.

Information Disclosure Statements

The Office Action Information Disclosure Statements filed September 15, 2005, November 22, 2005, and February 27, 2007, fail, in part, to comply with the provisions of 37 CFR §§ 1.97, 1.98 and MPEP § 609 because many of the PCT publications recite PCT rather than WO. The Examiner also indicates that the Information Disclosure Statement (IDS) filed on February 27, 2007 has not been fully considered because the Examiner the February 27, 2007 IDS is not in compliance with the requirement.

A Supplemental Information Disclosure Statement. listing the PCT applications indicating WIPO rather than PCT as the country code and providing a listing of Office Actions and documents cited in related US and foreign patent applications, has been mailed via Express mail on the same day herewith under separate cover. The supplemental Information Disclosure Statement includes the application number of the application in which it is submitted, a column that provides a blank space next to each citation for the Examiner's

initials, and a heading on the listing that clearly indicates the list is an Information Disclosure Statement, and copies of each cited Office Action. There is no requirement to list all material that is cited to the Office on a form PTOL-1449. A listing of commonly owned or jointly invented applications and/or other information provided to the Office for consideration is not required to be listed in a form PTOL-1449, since the information is provided, but not intended to be listed on the face of the patent. Therefore, this supplemental Information Disclosure Statement is in compliance with 37 CFR §§ 1.97, 1.98 and MPEP § 609. Consideration of all information provided respectfully is requested.

Objections to the Claims

Claims 157 and 173 are objected for minor informalities. Cancellation of claim 157 as duplicative of claim 1 renders this objection moot with respect to claim 157. Cancellation of claim 173 as non-elected renders the objection moot.

THE REJECTION OF CLAIMS 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160. 161, 163. 164, 166, 169 and 173 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160. 161, 163. 164, 166, 169 and 173 are rejected under 35 U. S. C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and/or the following remarks.

Relevant law

The purpose of 35 U.S.C. §112, second paragraph, is to provide those who would endeavor, in future enterprise, to approach the area circumscribed by the claims of a patent, with adequate notice demanded by due process of law, so that they may readily and accurately determine the boundaries of protection involved, evaluate the possibility of infringement and dominance by determining the metes and bound of protection so one can evaluate the possibility of infringement with a reasonable degree of certainty. *In re Hammack,* 427 F.2d 1378, 166 USPQ 204 (CCPA 1970). Claims are not to be read in a vacuum, and the limitations therein are to be interpreted in light of the specification, giving them their broadest reasonable interpretation. When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite. Rosemount Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1,

7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983).

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

"Obviously, however, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. Ex parte Porter, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface." M.P.E.P. § 2173.05(e). Relevant law avoids an absolute requirement for antecedent basis when the when the specific context is clear. Just as "the outer surface of said sphere" is clear, the cytoplasm of the cell is clear. Applicants submit that the context of "the cytoplasm" in the phrase "the cytoplasm of the cells" is clear to one of skill in the art.

Analysis

A. Claim 1, which recites "the resulting complexes of biomolecules/capture compounds" in line 5, is rejected as allegedly providing insufficient antecedent basis for this recitation in the claim. Claim 1 and all dependent claims are rejected under 35 USC 112, second paragraph.

As discussed above, relevant law avoids an absolute requirement for antecedent basis when the when the specific context is clear. Just as "the outer surface of said sphere" is clear, the resulting complexes of biomolecules/capture compounds" is clear. It respectfully is submitted that one of skill in the art would understand recitation in the claim that X binds covalently to biomolecules provides antecedent for the "resulting complexes of biomolecules/capture compounds." Amendment of claim 1, however, renders this ground of rejection moot.

B. Claim 1, which recites "the interaction between the capture compounds and the biomolecules" in lines 14 and 5, allegedly fails to provide antecedent basis for this recitation in the claim. As discussed above, relevant law avoids an absolute requirement for antecedent basis when the when the specific context is clear. Just as "the outer surface of said sphere" is clear, the recitation of "the interaction between the capture compounds and the biomolecules" is clear to one of skill in the art the recitation in step a) of "contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules" results in an interaction between a capture compound and biomolecule, thereby providing antecedent for the rejected language.

To advance prosecution, however, "the" has been deleted, thereby rendering the rejection moot.

C. Claim 10 is rejected for failing to provide proper antecedent basis for "the surface or a molecule thereon" in lines 2 and 3. While the above-quoted relevant law is directly on point, amendment of claim 10 to recite surface <u>of the support</u> obviates this rejection. One of skill in the art would understand that that a support has a surface.

D. Claim 163 is rejected as failing to provide proper antecedent basis for "the mass spectrometry format" in lines 1 and 2. One of skill in the art would understand mass spectrometric analysis provides antecedent for "mass spectrometry format" since mass spectrometric analysis is performed by mass spectrometry. In the interest of advancing prosecution, however, the claim is amended to recite "mass spectrometric analysis format."

E. Claim 164 is rejected as failing to provide proper antecedent basis for "the detection format" in line 1. As with claim 163, the relevant law is directly on point; one of skill in the art would understand that the detection format is a mass spectrometric analysis detection format. In the interest of advancing prosecution, however, the claim is amended to recite "mass spectrometric analysis detection format."

THE REJECTION OF CLAIMS 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110 116, 137, 139, 140, 144, 150, 151, 152. 157. 158, 159, 160, 161, 163, 164, 166, 169 and 173 UNDER 35 U.S.C. §112, FIRST PARAGRAPH- SCOPE

Claims 1,2, 6, 10, 15, 25, 34, 38. 43, 75, 110 116, 137, 139, 140, 144, 150, 151, 152. 157. 158, 159, 160, 161, 163, 164, 166, 169 and 173 are rejected under 35 U. S. C. §112, first paragraph, because the specification, while enabling for a limited number of X, Y, Q and Z substituents like biotin, small molecular weight drugs of known composition, a select number of known "latent" photoactivatable groups like azides, allegedly does not

reasonably provide enablement for the use of "any" X, Y, Q and Z." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner details the factors set out in In re Wands, 858 F. 2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and discussed below to support this rejection. This rejection respectfully is traversed.

Relevant Law

Enablement is a legal determination that assesses whether a specification teaches one of skill in the art to make and use what is claimed. Enablement is not precluded even if some experimentation is necessary, as long as the amount of experimentation is not undue. Atlas Powder Co. v. E. I. Du Pont De Nemours Co., 750 224 USPQ 409, 3 (Fed. Cir. 1984); W. L. Gore and Associates v. Inc., 721 220 USPQ 303, 315 (Fed. Cir. 1983).

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible, as long as it is not undue. To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything **within the scope** of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original.

The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen-fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) ("The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention"); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835, 225 USPQ 232 (1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the

> enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); *see also In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim .... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

Analysis

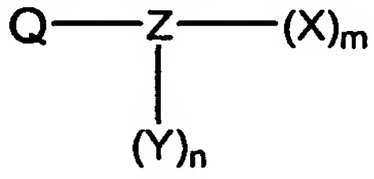
To establish undue experimentation, a consideration of the "*Wands* factors" as a whole is warranted. In this instance, as discussed below, an assessment of the *Wands* factors, which include the nature of what is claimed, the breadth of the claims, the teachings in the specification, the quantitation of experimentation necessary, the guidance provided by the specification, the presence of working examples, the state of the art, the knowledge of those of skill in the art and the level of predictability in the art, leads to the conclusion that one of skill in the art can practice the methods as claimed without undue, experimentation.

a. The breadth of the claims and nature of the claimed subject matter

Claim 1 is directed to a method for identifying targets and non-targets of a drug by:

> (a) contacting a capture compound that presents a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug with a sample containing biomolecules for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium;
>
> (b) activating X to form a covalent linkage or high affinity bond between X and biomolecule(s) in the sample that interact with Y to effect capture thereof; and
>
> (c) isolating and identifying the captured biomolecules, wherein the captured biomolecules comprise drug targets and non-targets.

The capture compounds are of formula:



in which

Z is a moiety for presenting X, Y and Q;

X is selected to covalently bind to biomolecules and requires activation following contacting with the biomolecules to effect covalent binding of the capture compound to a biomolecule;

Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug;

Q is a sorting function;

m is an integer that is 1 to 100; and

n is an integer from 1 to 100.

Dependent claims specify particulars regarding Z, Y, X and Q as well as the method, including additional steps, such as redesign of the drug to reduce interaction with drug non-targets.

As described in the application and claimed, the methods claimed in this application are methods for identifying molecules in a sample with which a drug, drug fragment, drug metabolite and/or prodrug interacts. Such molecules will include the targets for the drug and also any so-called non-targets with which a drug may interact. Non-targets can be responsible for side-effects or lack of specificity of particular drugs. Identification of such non-targets can aid in understanding a drug's activity and/or aid in redesign to eliminate such interactions. Identification of targets can be of interest for drugs whose targets are not known.

Thus, in practicing the method, the capture compound or compounds are contacted with a sample, such as a cell or tissue sample, under conditions such that the interactions with Y reach equilibrium. The compounds are then exposed to conditions in which X covalently binds or binds with high affinity to the biomolecules that interact with Y and capture them. The captured biomolecules can then be identified. For example, if Y is a drug, a drug typically has a target. When contacting the compound(s) with a cell or tissue sample, Y should interact with its target. In addition, in this method, the capture compounds also will capture non-targets with which Y interacts. Identification of such non-targets can be used to predict side-effects and to aid in design of drugs that have reduced interaction with non-targets, and, hence fewer side-effects. The method can be used to assess affinities (*i.e.*, Kd of a drug, drug fragment, drug intermediate, drug metabolite or prodrug with its target and/or non-target.

The compounds also can include a Q moiety for sorting compounds, such as for capturing them on a solid support, and optionally include a W moiety that can alter solubility properties of compounds so that they can interact with biomolecules in a sample in various environments, such a hydrophobic environment that exists in a cell membrane, or a hydrophilic environment. Hence the instant methods can probe selected environments depending upon properties of the capture compounds conferred by W.

. As discussed above, the methods assess the interaction of biomolecules in a sample with a moiety, Y, which is a drug, drug fragment, drug intermediate, drug metabolite or prodrug whose interactions with biomolecules are of interest. **Hence Y is selected by the user.** The method requires that the interaction of the biomolecules with the capture

compounds is performed under conditions such that the Y moieties reach equilibrium with biomolecules in a sample; then covalent or high affinity binding is effected between any such biomolecules and X, the reactivity function, to capture the biomolecules that interact with Y.

Z is any core, such as a molecule or solid support, for presenting X and Y. For practicing the method, X and Y, as well as Z, can be selected as described in the application. Selection of Y depends upon the molecule(s) whose interactions is/are selected for assessment. Hence the practitioner of the method selects Y. X has to be a molecule that will capture the biomolecules that interact with Y with sufficient affinity or by covalent bond to be stable for analysis. The claim specifies that biomolecules are capture by X either by covalent linkage or a linkage stable during mass spectrometric analysis. The specification provides detailed and extensive description of Z moieties, and X moieties as well as examples Y moieties.

The claims are not directed to compounds, but are directed to methods. The methods involve employing compounds with two functional moieties – one that is selected by a user to be assessed, and a second that forms covalent attachment or high affinity linkage to a biomolecule, such as a protein. As discussed in great detail below, the application provides examples of practice of the method as claimed.

b. The level of skill in the art and knowledge of those of skill

Applicant respectfully submits that the skill in the art of chemical synthesis is high, and is so-recognized by the Examiner. Similarly, the knowledge of those of skill in the art is extensive. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Synthetic schemes describing the synthesis of the disclosed compounds are provided in the specification.

c. The state of the prior art

There is extensive prior art in which capture compounds that present X moieties are used to capture biomolecules in samples. Such art is of record in this application. See, *e.g.*, , Hutchens *et al.* (WO 98/59360), Cravatt *et al.* (WO 01/77668 and WO 01/77684), and Coull *et al.* (EP 0424 819), which are of record in this application. The capture compounds

described in such publications, while not described for use in the instantly claimed methods, nor presenting a "Y moiety," as required by the instant claims, include moieties, designated X herein, for covalent capture of biomolecules. They also contain a core "Z" that presents X. Hence, those of skill in the art are well-acquainted with Z moieties and X moieties suitable for use in the compounds for use in the instantly claimed methods.

Further, as stated above, Y is user selected drug, drug fragment, drug metabolite or prodrug. Q is for arraying or immobilizing compounds. The above-noted exemplary publications, as well as describe such groups. Methods in which compounds are immobilized are well-known.

d. Teachings in the application and the presence of working examples

As discussed above, the methods claimed in this application are methods for assessing interactions of selected molecules or moieties (Y) with biomolecules in a particular cell, tissue or other sample. The instantly claimed embodiments are those in which Y is a drug, drug fragment, drug metabolite, prodrug. The method involves providing a compound(s) that present molecules or moieties Y to identify biomolecules in a sample with which Y interacts The X moieties are selected to covalently bind upon activation of the X to capture biomolecules that interact with Y. For example, if Y is a drug, then contacting it with sample from a biological fluid or cell sample can assess with what else, in addition to the drug target, the drug interacts. The non-targets can be responsible, for example, for side-effects. Dependent claims include further steps of redesigning the drug to eliminate or reduce interactions with non-targets, and thereby reduce undesirable side-effects.

In practicing the methods, the capture compound or compounds are contacted with a sample, such as a cell or tissue sample, under conditions such that the interactions with Y reach equilibrium. The compounds are then exposed to conditions in which X covalently binds or binds with high affinity to the biomolecules that interact with Y and capture them. The captured biomolecules can then be identified. For example, if Y is a drug, a drug typically has a target. When contacting the compound(s) with a cell or tissue sample, Y should interact with its target. In addition, in this method, the capture compounds also will capture non-targets with which Y interacts. Identification of such non-targets can be used to predict side-effects and to aid in design of drugs that have reduced interaction with non-targets, and, hence fewer side-effects.

The compounds also include a Q moiety for sorting compounds, such as by capturing them on a solid support, and optionally include a W moiety that can alter solubility properties

of compounds so that they can interact with biomolecules in a hydrophobic environment, such as a cell membrane, or a hydrophilic environment. Hence the instant methods can probe selected environments depending upon properties of the capture compounds conferred by W.

Also, as noted, the method is designed to assess biomolecules, such as proteins, that interact with Y groups, such as drugs, drug fragments, drug metabolites. The Y group interacts with molecules in a sample and reaches equilibrium. X is selected to form a covalent bond, such as by activation with the biomolecule with which Y interacts. This permits assessment of the molecules with which Y interacts. This can be used, for example, to identify so-called non-drug targets and to assess affinities of a drug with its target and non-targets. A particular drug is designed to target a molecule, such as a receptor or ligand. Interaction of a drug or its metabolites or fragments interact with other molecules besides the target can lead to side effects. The method permits identification of biomolecules with which such drugs, metabolites or fragments interact, thereby permitting redesign of drugs to reduce or alter such interactions and/or study of drugs to identify targets.

For practicing the method, X and Y, as well as Z, can be selected as described in the application. Selection of Y depends upon the molecule(s) whose interactions is/are selected for assessment. Thus Y is user selected. For practicing the method, X and Y, as well as Z, can be selected as described in the application. The application provides a detailed description of exemplary Z molecules, and provides examples of the practice of the method at for example, at page 92- page 93, page 94, line 29, - page 102, in Example 16 and elsewhere in throughout the specification as well as X and Q moieties.

The pending claims are based on the detailed description in the application, the original claims, description in the Examples, including Examples 14 and 16, and the depiction in Figure 30 and data in Figures 31-38. The original claims set forth the method. Example 30 depicts the method. Example 14 and Figures 31-38 describe and show practice of steps of the method. Disclosure in the specification describes the method and provides exemplary capture compounds that present a variety of drugs. Example 16 explains in great detail how particular family of drugs can be studied using the method. Example 16 shows the structure of capture compounds used in the method and also identifies metabolites and capture compounds containing metabolites. The Example identifies cells from which extracts and be prepared and incubated with the capture compounds, as in Figures 33-38. The captured products can be detected as in Figures 33-38. Therefore, the application provides detailed description for practice of the methods as claimed, including detailed

Examples.. The application teaches and demonstrates how to practice the method as claimed and shows that capture compounds prepared as described can be used to capture molecules that interact with a Y moiety that is user selected, such as a drug or drug metabolite or drug fragment.

The specification details embodiments in which Y is molecule, such as a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite prodrug that is used to identify targets and non-targets in a sample. For example at pages 6-7 of the specification, which describe embodiments in which drugs, drug fragments and other drug molecules are presented on the capture compounds to determine molecules in a sample that interact therewith to identify targets and non-targets:

> The capture compounds, collections and methods provided herein also permit screening of biomolecules, including but not limited to receptor proteins and enzymes, which are drug targets and non-targets, as defined herein, that interact with pharmaceutical drugs under physiological conditions. The screening of biomolecules provides increased understanding of the mechanism of action of the pharmaceutical drugs or drug fragments, metabolites or synthetic intermediates in the drug syntheses, thereby helping the design of more target specific drugs. The methods also provide for identification of non-target biomolecules, such as proteins including but not limited to receptors and enzymes, that interact with pharmaceutical drugs, thereby causing side effects and other undesired therapeutic effects. In one embodiment, various attachments of the drugs or drug fragments, metabolites or synthetic intermediates in the drug syntheses to the capture compounds are used to determine which functionalities of the drugs or drug fragments, metabolites or synthetic intermediates in the drug syntheses interact with the target and non-target biomolecules. In one embodiment, the non-target functionalities are then eliminated from the drug, resulting in an improved drug that exhibits fewer side effects. In another embodiment, a drug is included in the capture compound, proteins that interact with the drug are isolated and identified, the proteins are related to function, and the drug is re-engineered to eliminate or reduce interactions with non-target proteins. The method may be repeated on the re-engineered drug, as desired.

The specification at page 100, *et seq.*, states:

> Y is an enzyme inhibitor, an enzyme agonist or antagonist, a pharmaceutical drug or drug fragment, a prodrug or drug metabolite that modifies the selectivity of the capture compounds or collections thereof, to interact with the biomolecules or mixtures thereof, including, but not limited to specific receptors, to form covalent or non-covalent bonds with high affinity. In one embodiment, the capture compounds/ collections thereof have a selectivity function, which is a Cox-2 inhibitor, and a mixture of biomolecules contains Cox receptors among other biomolecules.
>
> In certain embodiments the selectivity function is selected from pharmaceutical drugs or drug fragments set forth below, where attachment of exemplary pharmaceutical drugs to a central core is shown below. In other embodiments, the selectivity function is a drug, drug fragment, drug metabolite, or a drug synthetic intermediate.
>
> The pharmaceutical drugs or drug fragments can be attached to the central core Z, in different orientations via different points of attachment, thereby modulating the selectivity of the capture compound. The attachment of a drug/drug fragment to the central core can be carried out by methods known to a person with skill in the art. Attachment of some exemplary pharmaceutical drugs at various points, to the central core Z is set forth below.

In another embodiment, the capture compounds provided herein include those where the selectivity function is a drug, drug fragment, drug metabolite or a prodrug. In these embodiments, the capture compounds also contain a reactivity function, as defined elsewhere herein. In further embodiments, the capture compounds also contain a sorting function, as defined elsewhere herein.

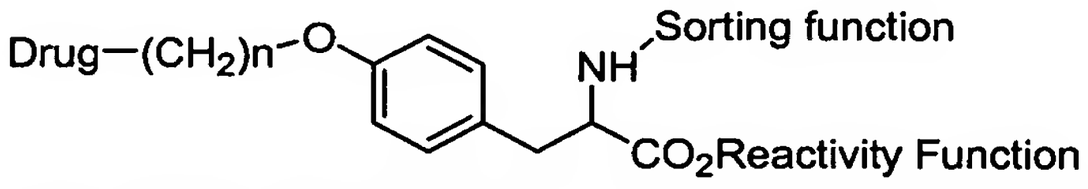
In certain embodiments, the capture compounds that contain drug, drug fragment, drug metabolite or prodrug selectivity functions contain an amino acid core. In one embodiment, the amino acid core may be an amino acid that does not have a functionality on the side chain for attachment of a third function. Such amino acid cores include, but are not limited to, glycine, alanine, phenylalanine and leucine. In these embodiments, the capture compound contains a reactivity function and a selectivity function, which are attached to the amino and carboxy groups of the amino acid.

On the following pages (pages 101-108), the specification provides examples of capture compounds in which Y is drug:

In another embodiment, the amino acid core may be an amino acid that possesses a functionality on the side chain for attachment of a third function. Such amino acid cores include, but are not limited to, serine, threonine, lysine, tyrosine and cysteine. In these embodiments, the capture compound contains a reactivity function, a sorting function and a selectivity function, which are attached to the amino, carboxy and side chain functional groups of the amino acid.

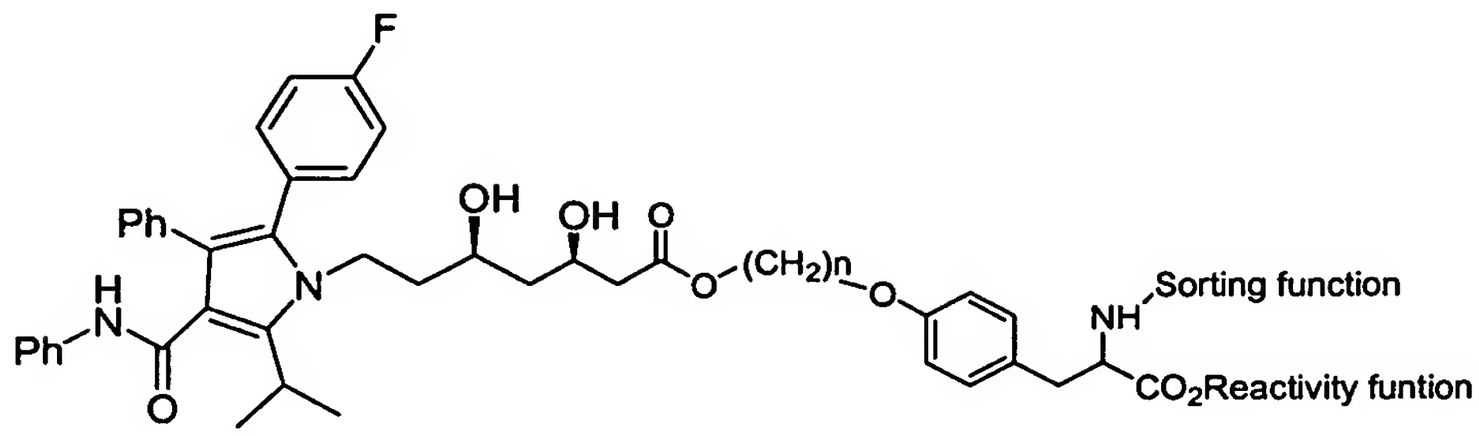
In another embodiment, the amino acid core may be an amino acid that possesses a functionality on the side chain for attachment of a third function. Such amino acid cores include, but are not limited to, serine, threonine, lysine, tyrosine and cysteine. In these embodiments, the capture compound contains a reactivity function, a sorting function and a selectivity function, which are attached to the amino, carboxy and side chain functional groups of the amino acid.

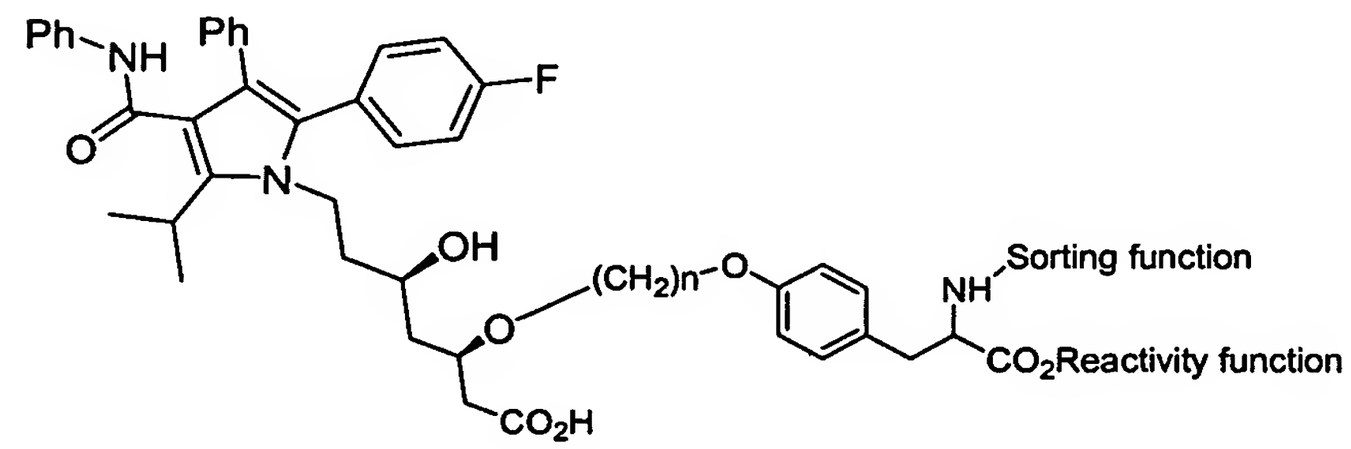
In one embodiment, the core is tyrosine and the capture compounds have the formula:

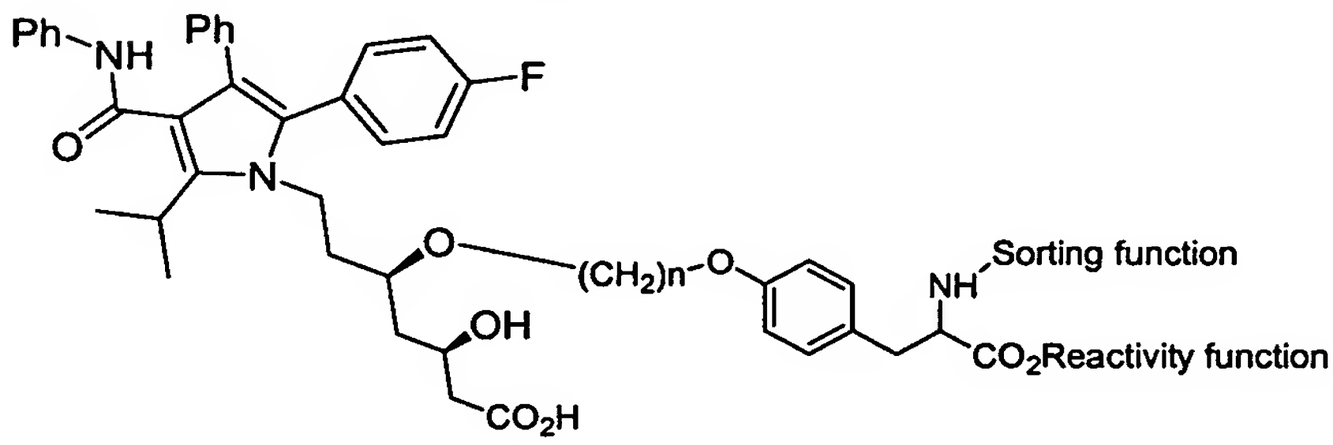


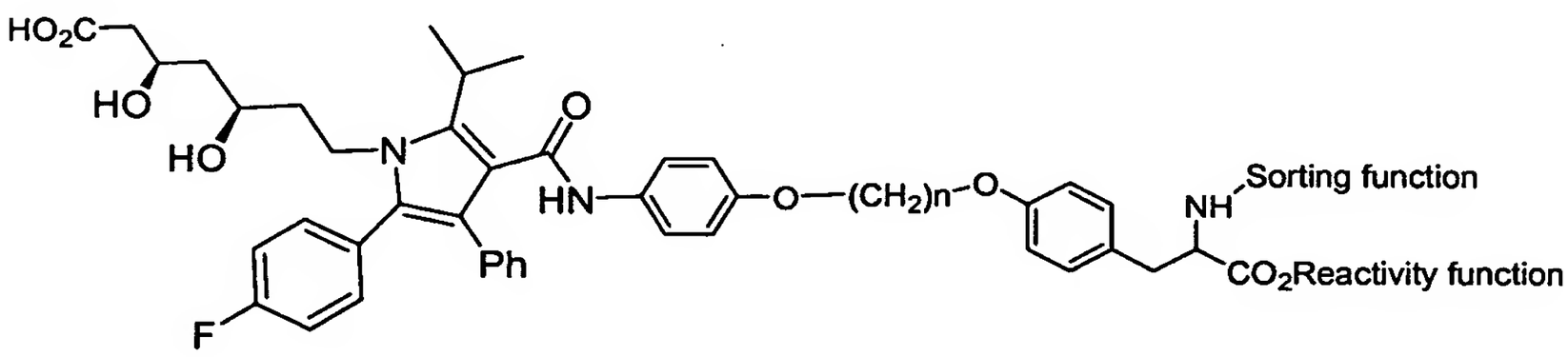
where "drug" refers to a drug, drug fragment, drug metabolite or prodrug.

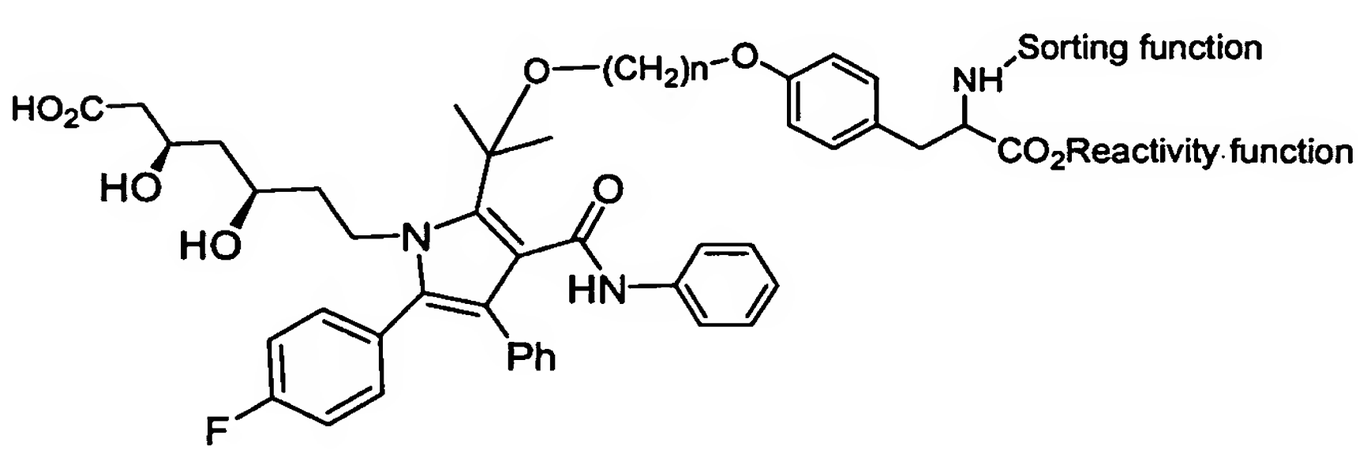
In one embodiment, the drug is LIPITOR® (atorvastatin calcium) and the capture compounds have the formulae:



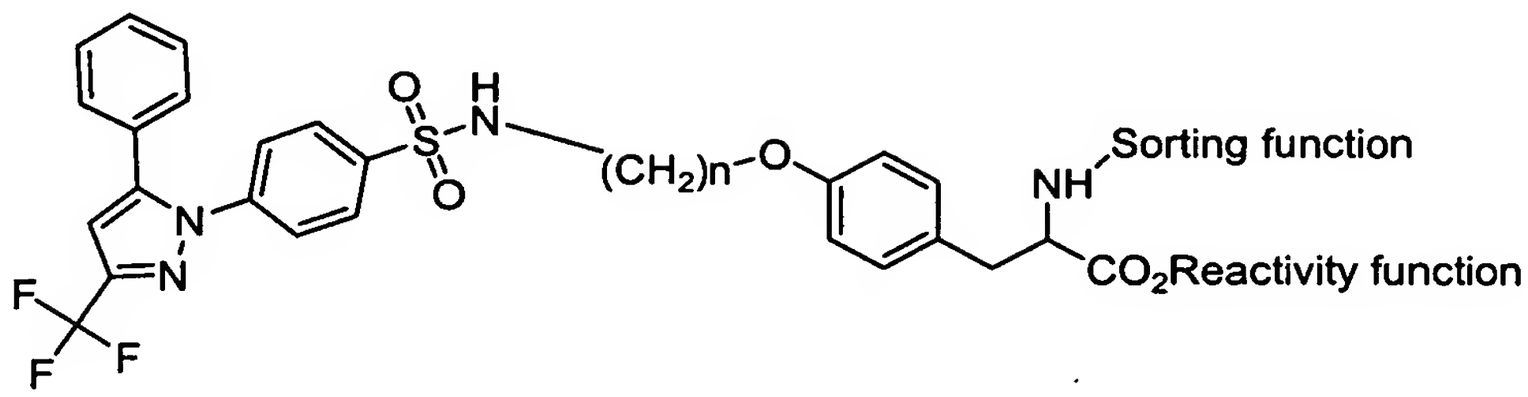


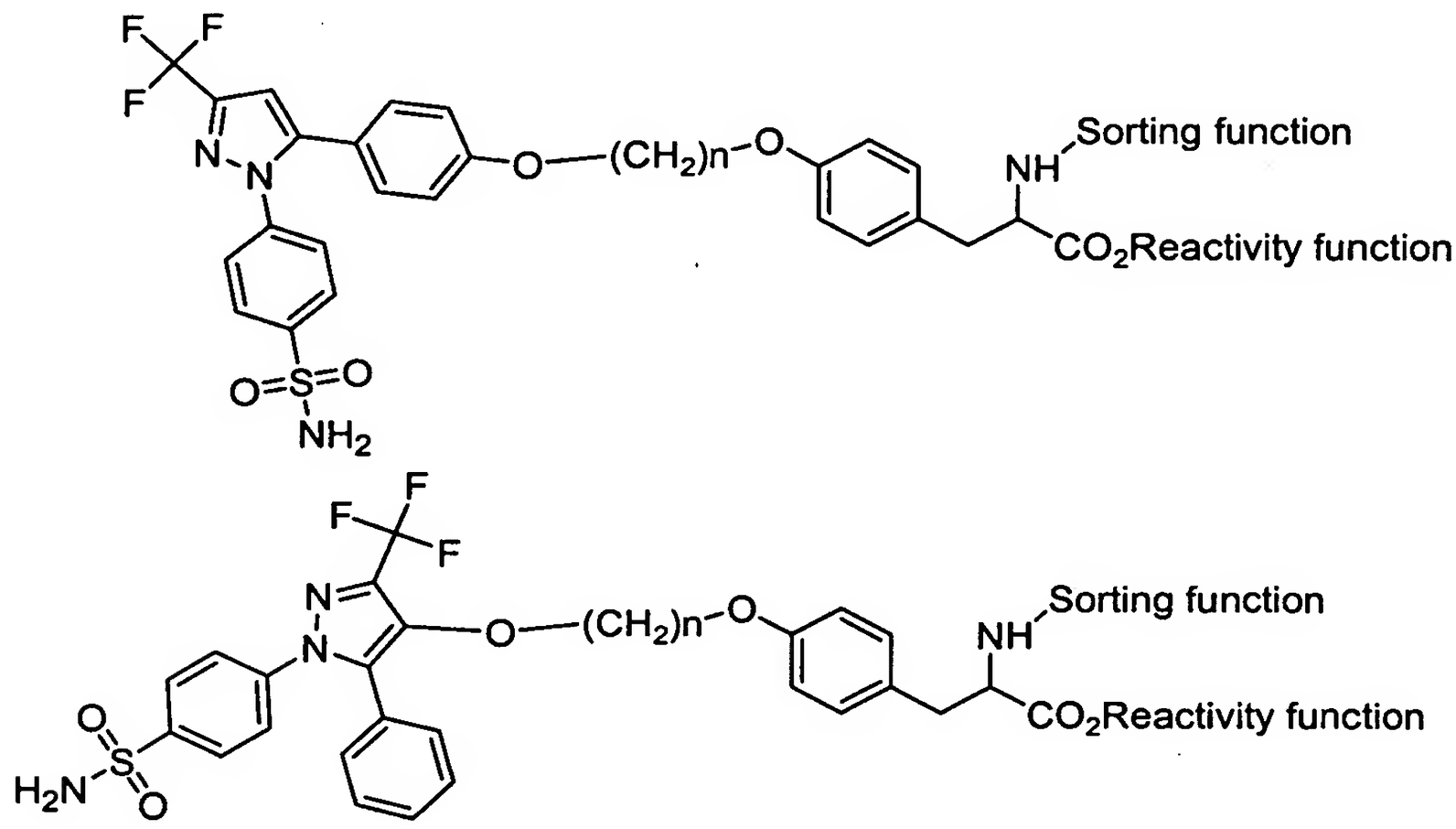




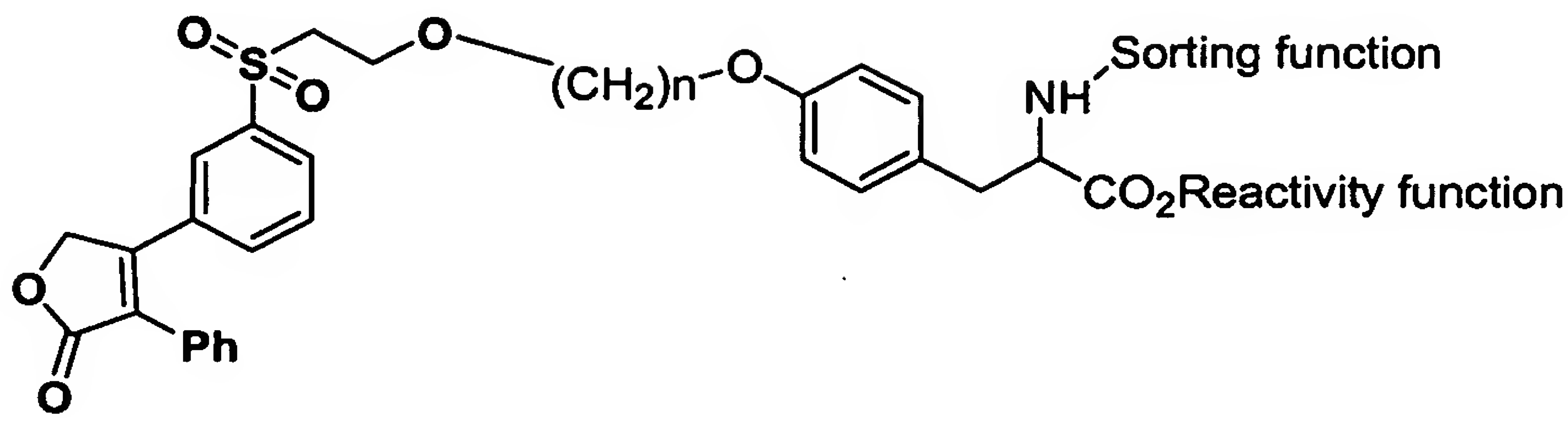


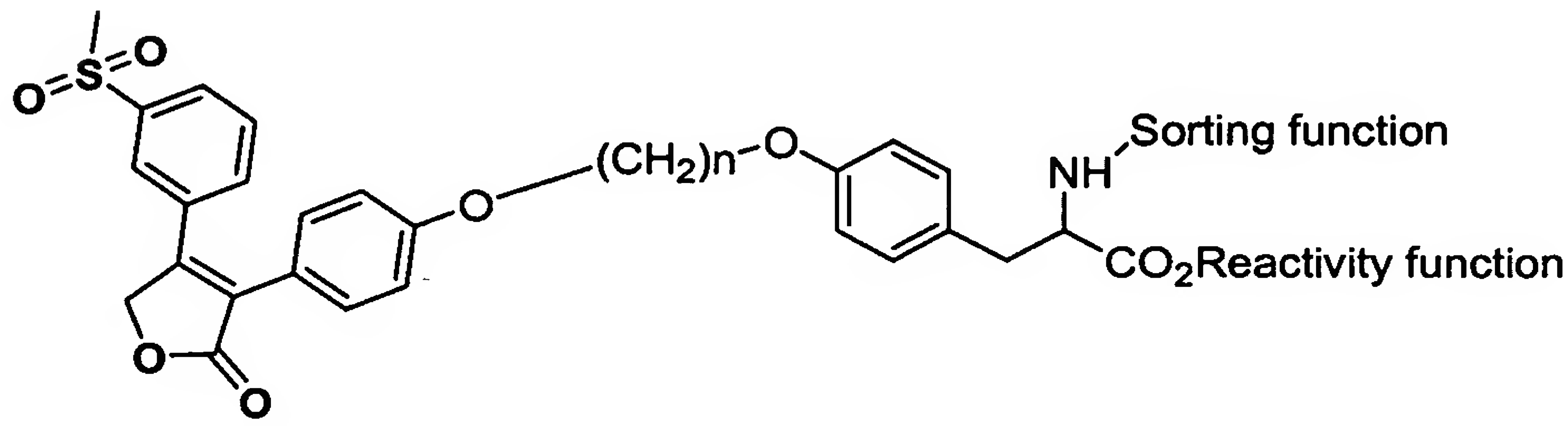
In other embodiments, the drug is CELEBREX® (celecoxib) and the capture compounds have the formulae:

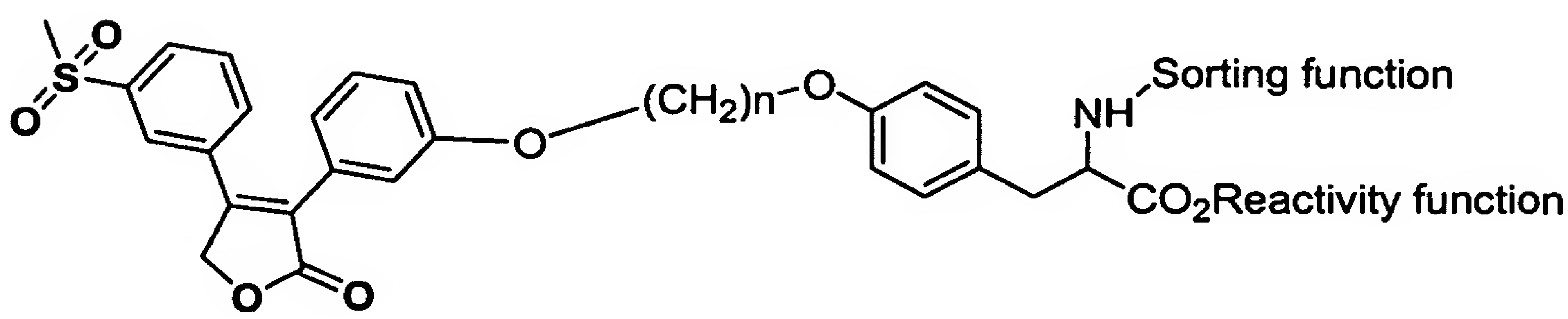


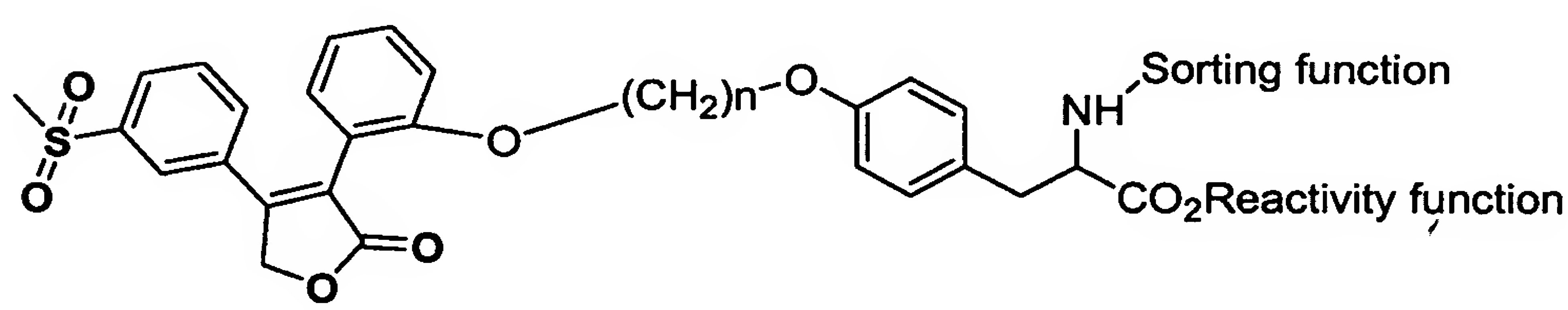


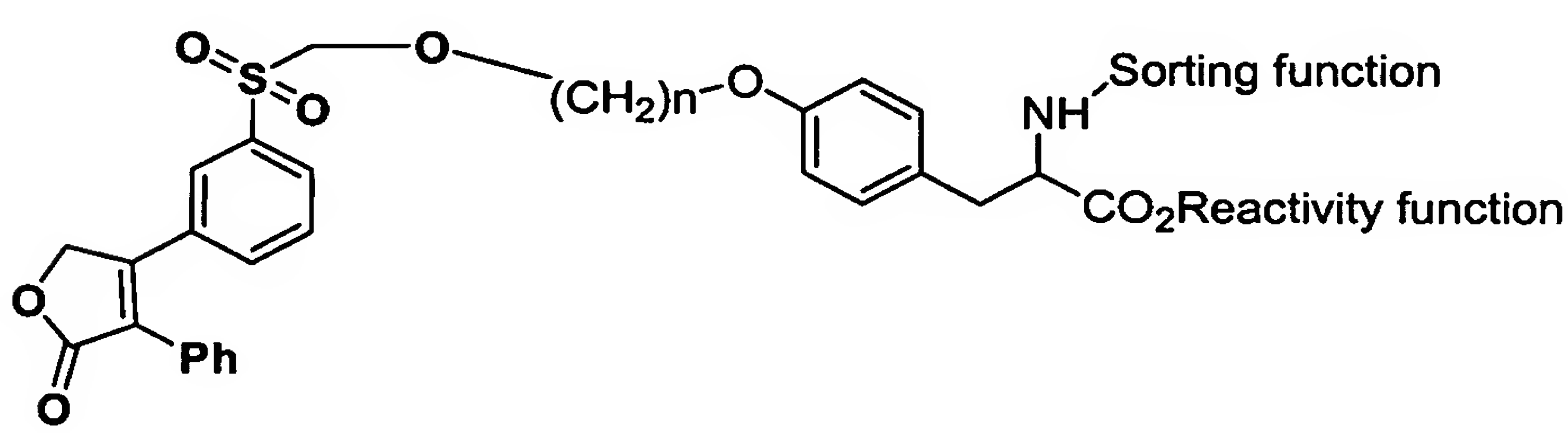
In another embodiment, the drug is VIOXX® (rofecoxib) and the capture compounds have the formulae:



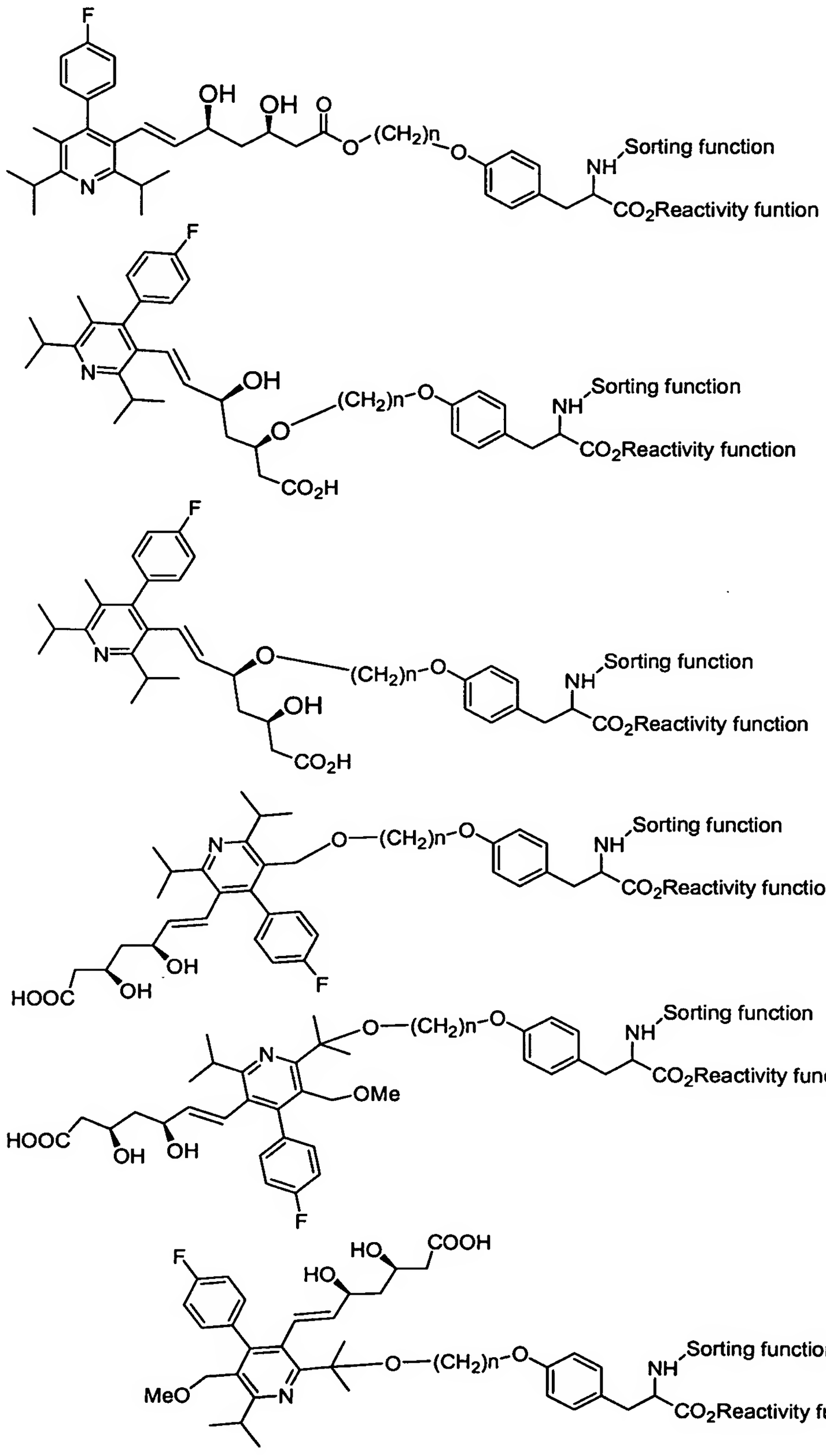




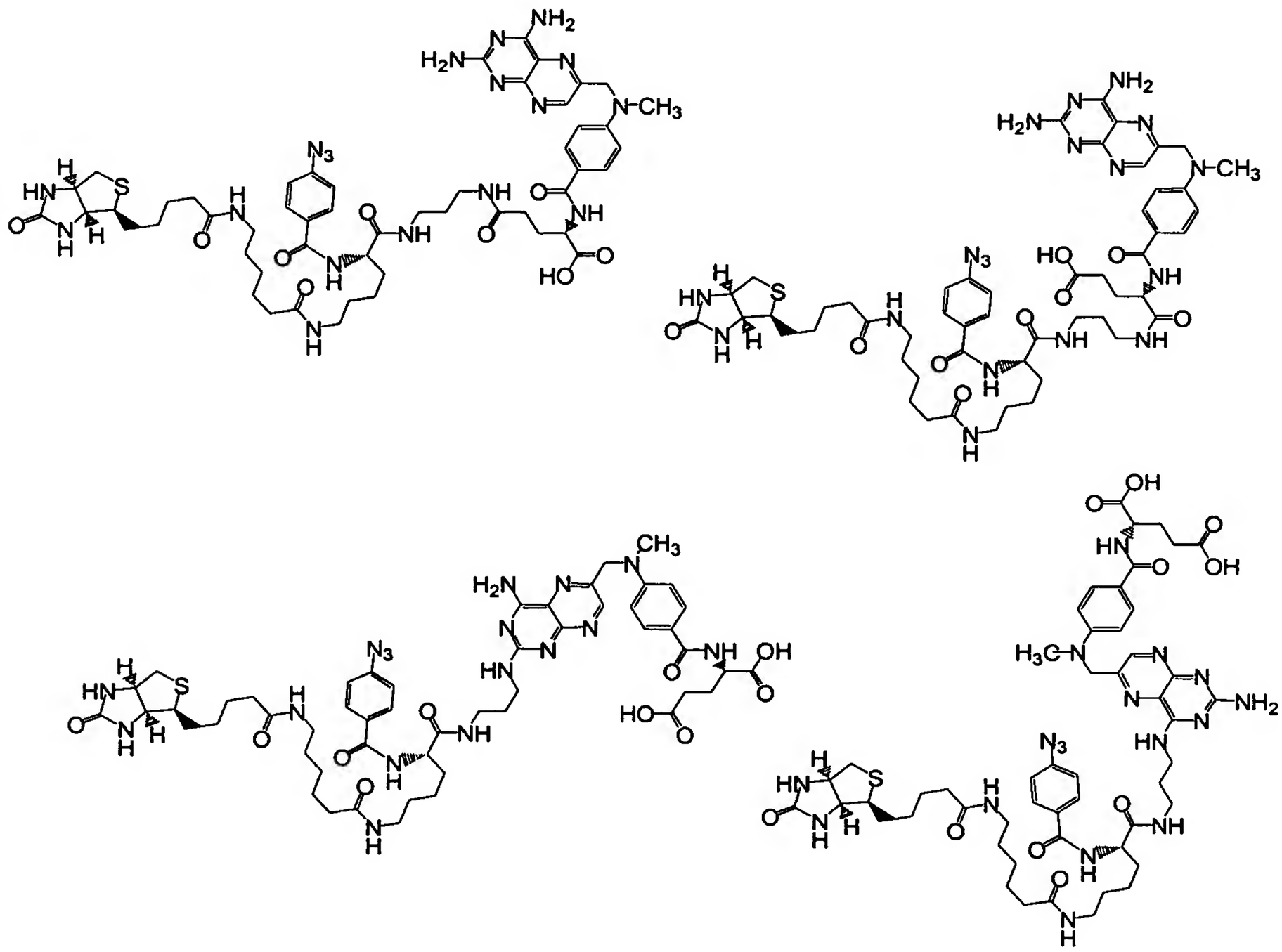




In another embodiment, the drug is BAYCOL® (cerivastatin sodium) and the capture compounds have the formula:


F
OH
OH
O
(CH2)n
O
NH
Sorting function
CO2Reactivity funtion
F
N
OH
(CH2)n-O
Sorting function
NH
CO2Reactivity function
CO2H
F
N
O
(CH2)n-O
Sorting function
NH
CO2Reactivity function
OH
CO2H
N
O—(CH2)n-O
Sorting function
NH
CO2Reactivity function
F
HOOC
OH
OH
F
N
O—(CH2)n-O
Sorting function
NH
CO2Reactivity function
OMe
HOOC
OH
OH
F
HO
COOH
HO
F
MeO
N
O—(CH2)n-O
Sorting function
NH
CO2Reactivity function

In another embodiment, the drug is methotrexate and the capture compounds have the formulae:



At page 113, the specification includes Y moieties listed in claim 2:

> . . . ligands that bind to receptors such as insulin and other receptors (see, e.g., the Table of ligands below); cyclodextrins; enzyme substrates; lipid structures; prostaglandins; antibiotics; steroids; therapeutic drugs; enzyme inhibitors; transition state analogs; specific peptides that bind to biomolecule surfaces . . .

Figure 30 and pages 49-50 and in Example 16 describe the method as claimed:

> In another embodiment, the analytical process (Figure 30) is simple and highly amenable to automation. First, a protein mixture from the cells of interest is incubated with a capture compound in buffer conditions which retain the native structural features of the proteins. The selectivity function [Y] reversibly interacts and comes to equilibrium with those proteins for which it has an affinity. The reactivity function [X] then forms a covalent bond irreversibly linking the compound to those proteins for which there was an affinity

The working Examples teach how to practice these methods and provide data showing practice each step of the method, namely: (1) contacting a capture compound with user-selected Y groups with a sample for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium, (2) activating X to form a covalent

linkage or high affinity bond with a biomolecule to effect capture thereof; and (3) identifying captured molecules is described and exemplified in the application.

Preparation of compounds and reactions in which molecules are captured and analyzed are detailed in the Examples . Examples 12 and 13 show how to make exemplary capture compounds for use in the method, and Example 14 shows that how to use a capture compound that presents a drug to capture a target molecule in a sample. Example 14 shows that an exemplary capture compound that presents a drug captures target (CAII) and non-target molecules in a sample. Example 15 provides another use for the methods. Example 16 exemplifies all steps in the method and describes use of the method for comparison of drugs in a particular class. Figure 30 and Example 16 describe in detail how to apply such to the instantly claimed method steps. The results in Figures 31-38 demonstrate reduction to practice of the method as claimed. Thus, all steps in the method are described and/or exemplified in the application.

The specification provides a detailed description of how to perform the method as claimed; the claims are not directed to new drugs but to a method whose steps are taught in great detail in the specification. Each step is well-within the level of skill in the art. The application teaches and has working examples detailing how to prepare capture compounds and incubate them and how to identify captured molecules, as claimed. The specification includes Figure 30, which schematically depicts the method, and Example 16 which is a step-by-step example for identifying structural features that contribute to pharmaco-logic/therapeutic profile and differences in activity within an exemplary class of drugs, the thiazolidinediones (such as Troglitazone (Rezulin™), Rosiglitazone (Avandia™) and Pioglitazone (Actos™)) and their metabolites. The specification also teaches and exemplifies synthesis of capture compounds and provides working examples showing capture and analysis of captured compounds. Other exemplary capture compounds that present drugs for analysis, are described throughout the disclosure, such as in the text reproduced above.

As noted above, the embodiments that presently are claimed are those in which Y is user selected and is a moiety, such as a drug or drug metabolite or other moiety (listed in claim 1) whose interactions are assessed. The overall process as claimed is depicted in Figure 30, which shows that a capture compound is mixed with a sample containing a mixture of proteins. Proteins or other biomolecules in a sample with an affinity for the Y (*i.e.*, drug) are allowed to come to equilibrium with the Y function. The X moiety in the capture compound is then activated (for example, with electromagnetic radiation) forming a

radical, which is short-lived, to covalently captures the proteins for which Y had an affinity. Proteins are not captured if the capture compound was not in very close proximity due to the equilibrium between Y function and such proteins. The capture compounds with captured protein are isolated, such is with biotin, and identified using mass spectrometry.

The results in Figures 31-38 demonstrate reduction to practice of the method as claimed. Figure 31 shows selective protein capture using capture compounds that present drugs whose interactions with a sample are assessed. Capture compounds A and B (page 124 of the application) contain a sulfonamide (a drug) that interacts with Carbonic Anhydrase (CA). Capture compound A presents a 4-sulfamoyl benzene carboxamide. Sulfonamides, such as these, are known inhibitors of carbonic anhydrase (CA), and are used as topical anti-glaucoma drugs. CAII is the target; CAI is non-target. Example 14 and Figures 31-38 demonstrate use of this compound in the method as claimed. These figures demonstrate isolation of CAII (target) as well as CAI (non-target) from complex mixtures, indicating that a capture compound, that presents a drug, such as a benzene sulfonamides not only bind to the targeted CAII, but also bind to non-target, related molecule, CAI, which could be a source of side-effects of these drugs.

The assays described in Example 14 were performed to determine the Kd. According to literature, the Kd of the sulfonamide for the CA II isoform is ~10 nM, and for the CA I isoform is ~1 uM. These values were independently confirmed using the assay as described in the Example, in which the capture compounds are incubated with a sample containing the CA isoform under conditions that allow it to reach equilibrium. The CA isoform is then captured using X. Using purified proteins, affinity and capture efficiency is highest for CA II, lower for CA I, and negligible for other purified proteins tested.

Figure 32 shows relative binding strengths of protein isoforms to a known ligand for capture compound B. Figure 33 shows isolation of Carbonic Anhydrase from complex protein mixtures using capture compound A. CA II was doped into a FPLC purified protein mixture from the human kidney cell line HEK293, The doped CAII was pulled out from all other proteins using avidin-coated (SoftLink) resin. Other proteins were discarded, yielding purified protein ready for further analysis. Figure 33 shows incubation of a capture compound that comprises a drug with a sample of purified proteins from a cell line that contains the target protein. The CAII was isolated and detected. Thus, Figure 33 shows practice of all steps of the method:) contacting a capture compound with user-selected Y groups with a sample for a sufficient time for the interaction between the capture compounds

and the biomolecules to reach equilibrium, (2) activating X to form a covalent linkage or high affinity bond with a biomolecule to effect capture thereof; and (3) identifying captured molecules is described and exemplified in the application.

Figure 34 shows isolation of Carbonic Anhydrase from a highly complex protein mixtures using capture compound A. CA II was doped into the whole cytosolic extract from the human kidney cell line HEK293, . The doped CAII was pulled out from all other proteins using avidin-coated (SoftLink) resin. Other proteins were discarded, yielding purified protein ready for further analysis. Figure 34 also shows practice of all steps of the method.

Similarly Figures 35-38 show practice of all steps of the method. Figure 35 shows capture and isolation of Carbonic Anhydrase from lysed red blood cells. The top spectrum in the figure shows direct MALDI of lysed red blood cells (no purification) wherein signal for Hemoglobin, which is in huge excess over all other proteins, can be seen. Signals are seen for the alpha and beta chains, and also for non-specific dimers (~30 kiloDaltons). The bottom spectrum in the figure is taken after capture compound A, containing a sulfonamide drug with an affinity for Carbonic Anhydrase, is mixed with the lysed red blood cells. The capture compound covalently captures the Carbonic Anhydrase isoforms I and II. All other proteins that are not covalently captured, including nearly all of the Hemoglobin which is in 2-3 log excess, are washed away prior to MALDI analysis. No gel or chromatographic cleanup is required to obtain this spectrum. The intensity of the CA II peak is higher than CAI (which is more ~100x more abundant in RBCs) because the sulfonamide drug has a higher affinity for CAII.

Figure 36 shows direct capture of Carbonic Anhydrase from red blood cells, without pre-lysis of the cells. Figure 37 shows capture of Carbonic Anhydrase from red blood cell lysate when unbiotinylated proteins including Carbonic Anhydrase are in huge excess. Figure 38 shows capture of proteins with lower affinities using very high concentrations of capture compound A.

Thus, these figures show that capture compounds that present drugs can be used to assess their interactions. Figures 31-38 show reduction to practice of each step of the method:) contacting a capture compound with user-selected Y groups with a sample for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium, (2) activating X to form a covalent linkage or high affinity bond with a biomolecule to effect capture thereof; and (3) identifying captured molecules is described and exemplified in the application

In addition, Example 16 provides a step-by-step example for identifying structural features that contribute to pharmacologic/therapeutic profile and differences in activity within a structural subclass, such as the thiazolidinediones, which are ligands of the PPAR-γ 2. PPAR-γ 2 predominantly is expressed in adipocytes, intestine, and macrophages and possibly muscle cells. Thiazolidinediones (Glitazones) include the drugs:Troglitazone (Rezulin™) Rosiglitazone (Avandia™) and Pioglitazone (Actos™). The anti-diabetic activity of thiazolidinediones is effected by binding to PPAR-γ (gamma) protein. Structure Activity Relationships (SARs) of thiazolidinediones and crystal structures of and PPAR-α co-crystallized with thiazolidinediones is known in the literature

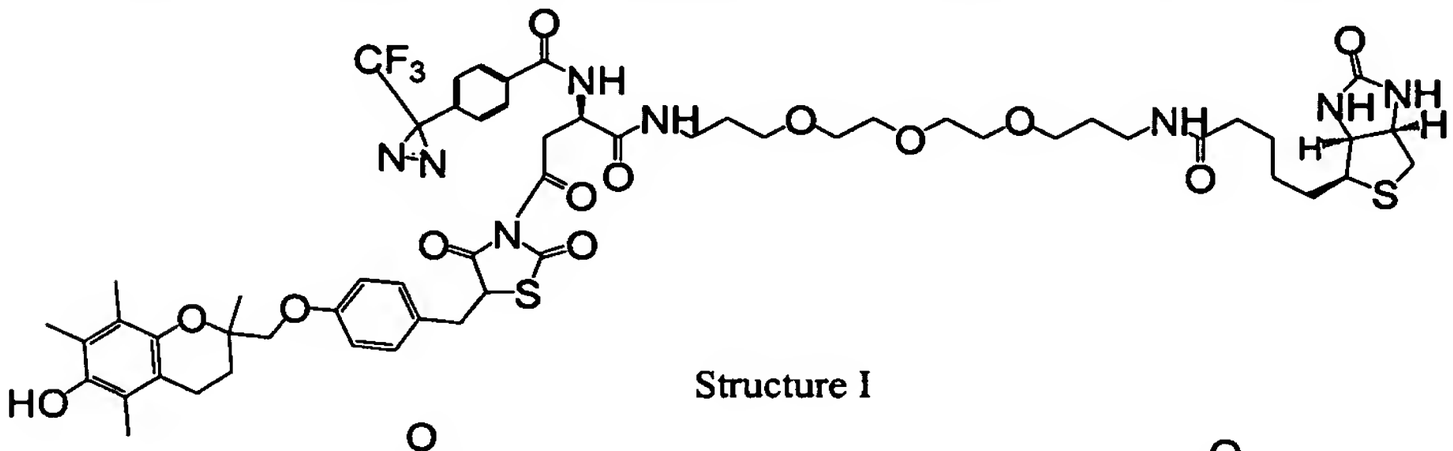
The effect of thiazolidinediones on insulin sensitivity is mediated through altered expression of PPAR-γ 2- dependent genes. Thiazolidinediones, as anti-diabetic drugs, exhibit show toxicity and undesirable side effects. Thiazolidinediones (Glitazones): Troglitazone (Rezulin™) Rosiglitazone (Avandia™) and Pioglitazone (Actos™) are attached Y groups that are attached to Z moiety in the capture compound. These are designated CC-Thiazolidinediones. These are incubated with kidney, liver, pancreatic, colonic epithelium and muscle cells, which are cells in which PPAR-γ is expressed. Rezulin, Avandia and Actos will capture PPAR-γ, PPAR-α and also any non-target proteins with which each interacts. Since these three drugs have different metabolism and pharmacokinetics, they will capture different non-target proteins.

Since undesired and toxic side effects of each of the thiazolidinediones can be due to interaction with PPAR-α and non-target proteins, identification of the captured non-target protein for each drug will provide insights into possible sources of side-effects. In addition, as described and claimed, the drugs then can be modified to eliminate these interactions. The modified drugs can be screened kidney, liver, pancreatic, colonic epithelium and/or muscle cells using these methods to confirm that the they are more specific for the PPAR-gamma target than the original drugs.

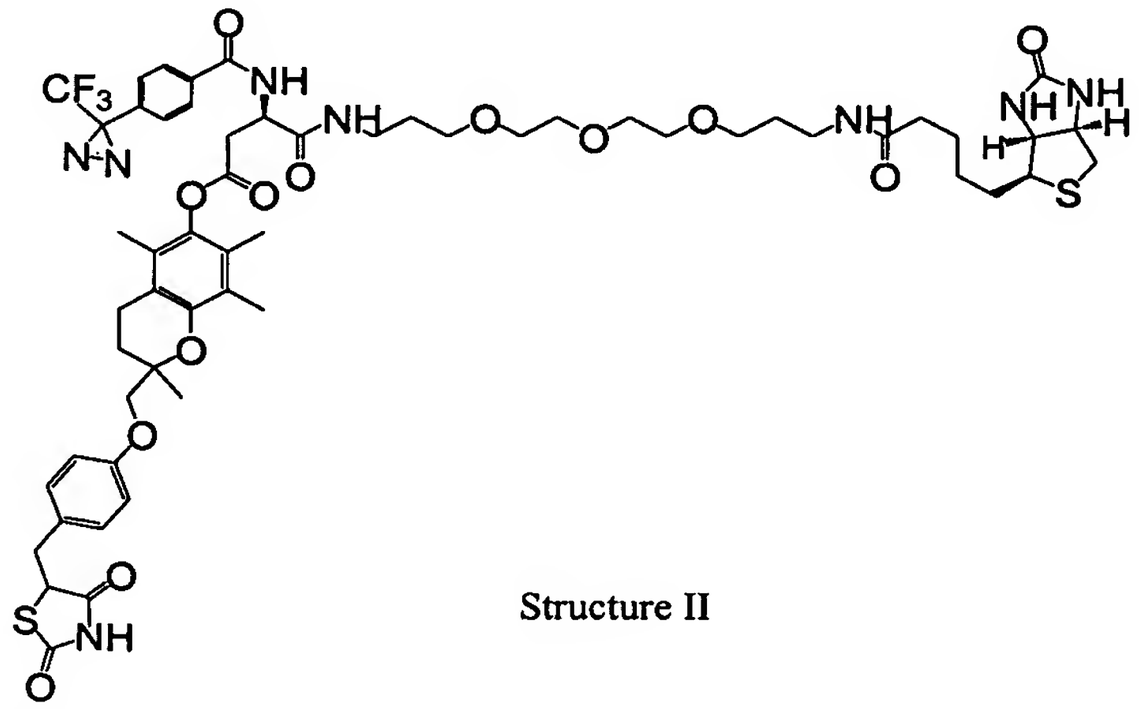
Example 16 describes this and also shows the structures of capture compounds (reproduced below) to be used in the method (incubation with kidney, liver, pancreatic, colonic epithelium and muscle cells for time sufficient to reach equilibrium, activation of the X group to capture the interacting molecules, and identification of the captured molecules. The other working examples in the application show that compounds have been prepared and that they will capture molecules and that mass spectrometry can be used to identify captured compounds. Description from Example 16 is reproduced as follows:

Rezulin:

Rezulin is attached to the Capture Compound as depicted below:



Structure I



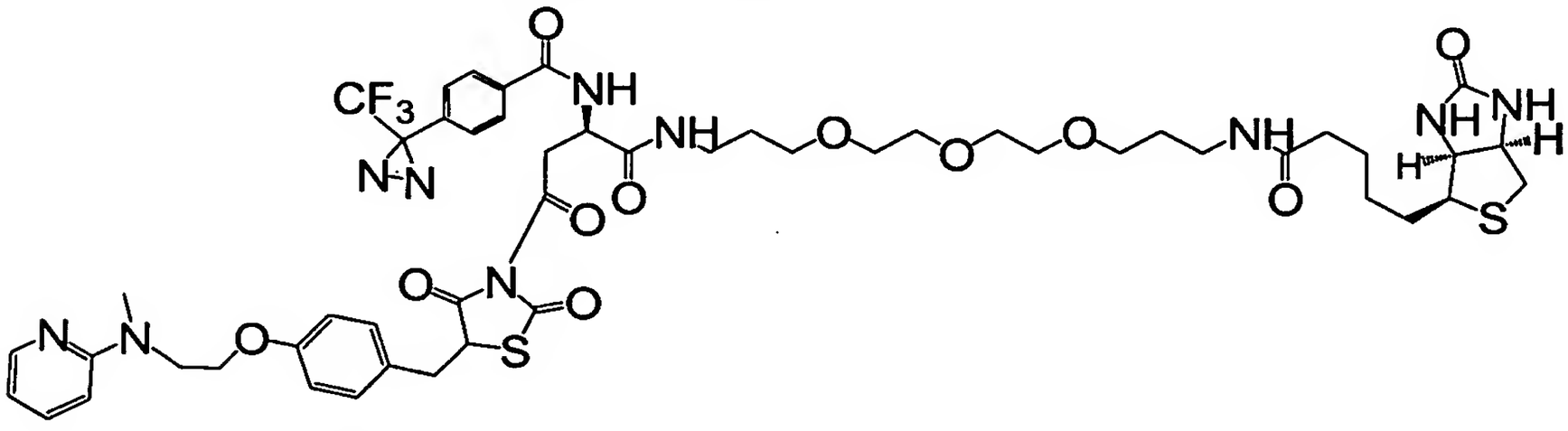
Structure II

Rezulin is metabolized in the liver to its p-Hydroxy glucose and sulfate complexes. Therefore Structure II is used.

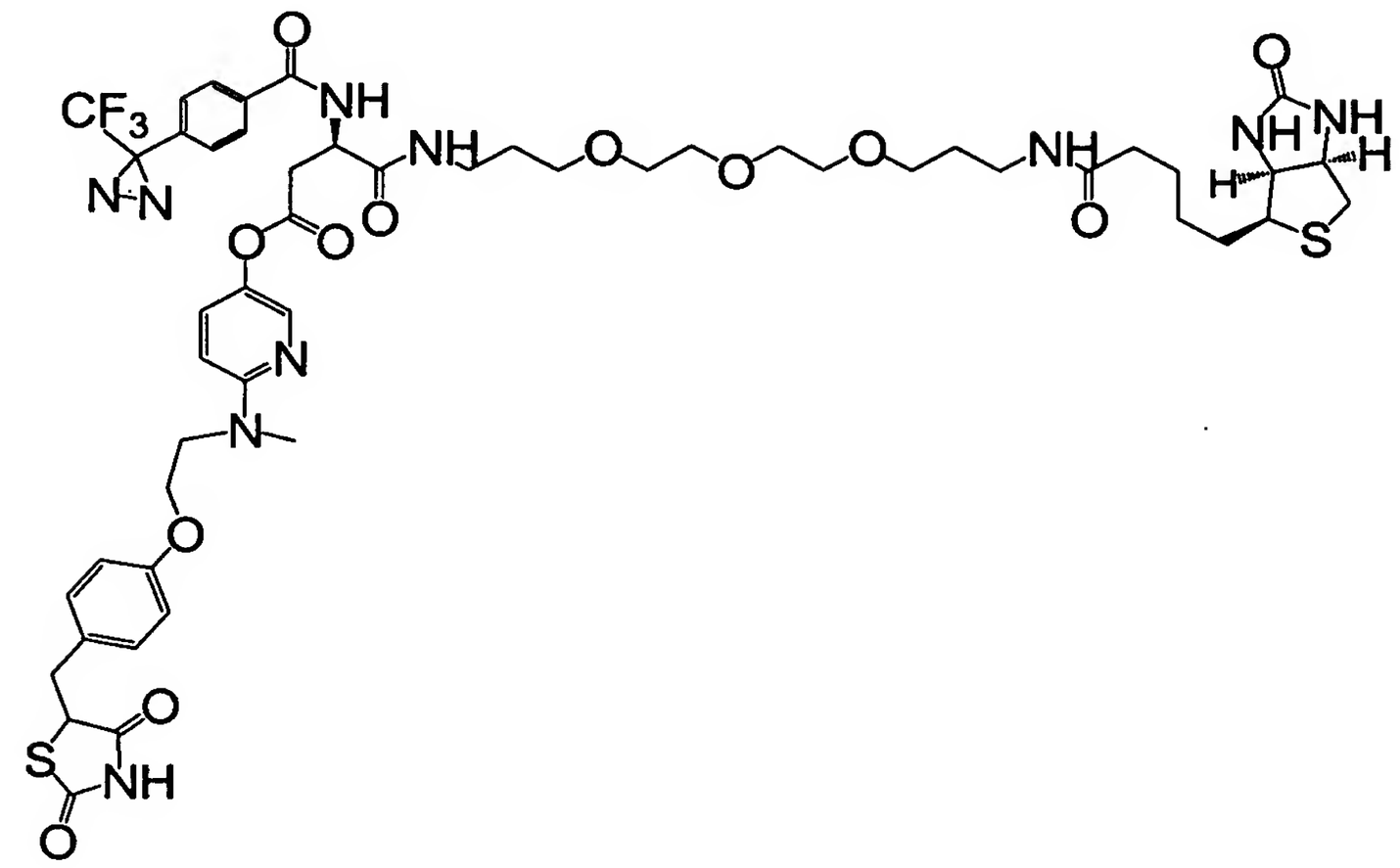
Rezulin Capture Compound Structures I and II are incubated with kidney, liver, pancreatic, colon epithelium, and muscle cells. The target protein PPAR-γ as well as non-target protein PPAR-α and protein A, B and C are captured.

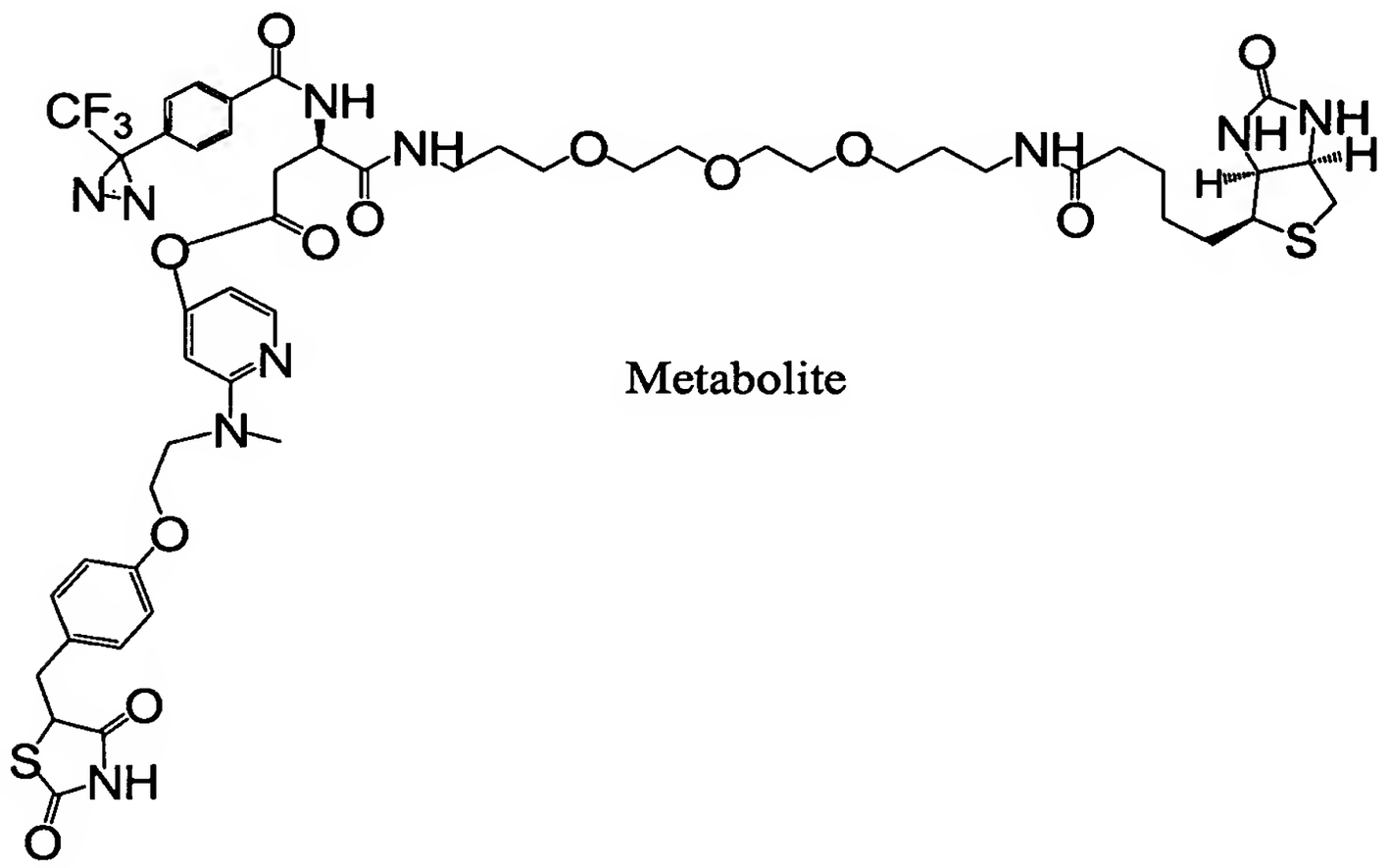
Avandia and Its Metabolite:

Avandia is attached to the capture compound as depicted below:

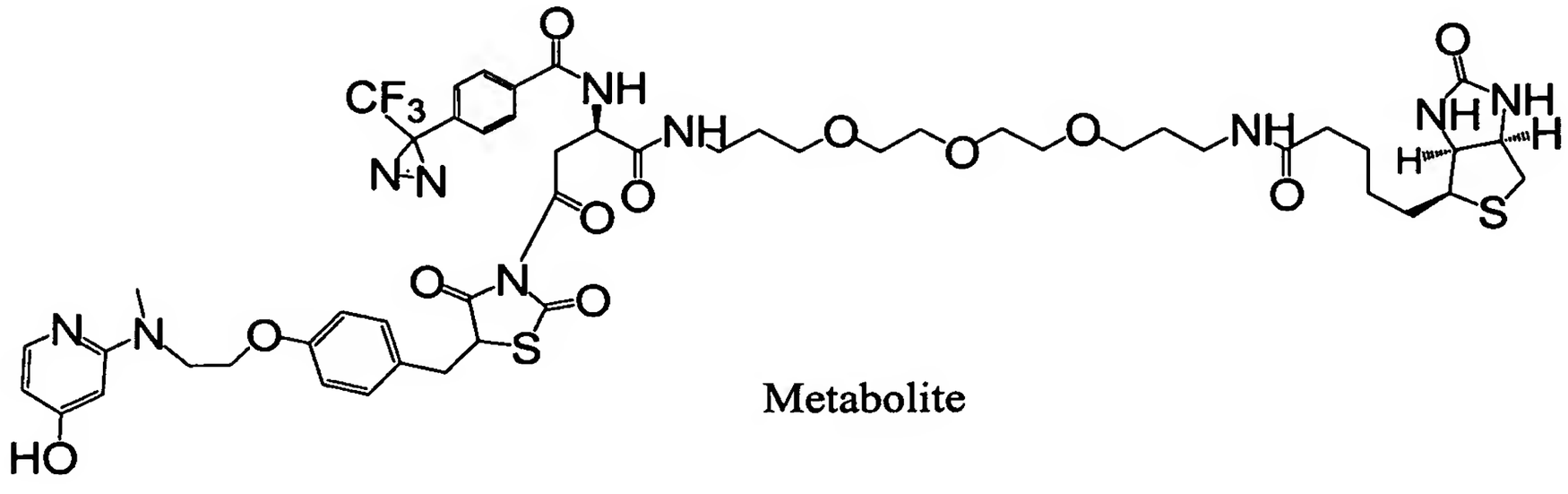


Avandia metabolizes to aromatic hydroxy metabolites. Therefore two possible metabolites are attached to the capture compound as depicted below:

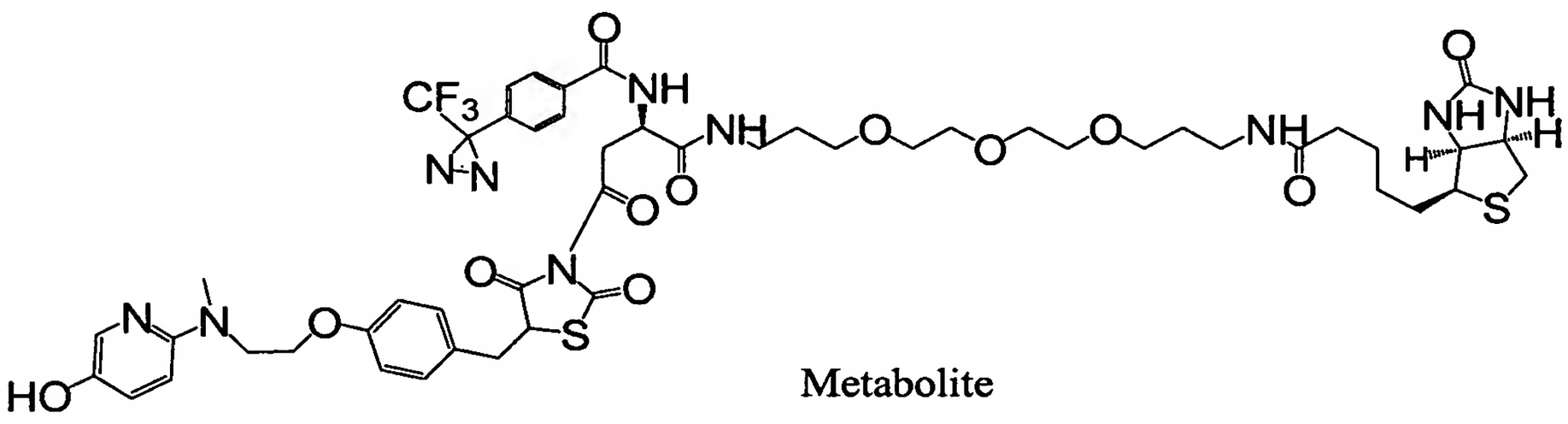




Metabolite



Metabolite

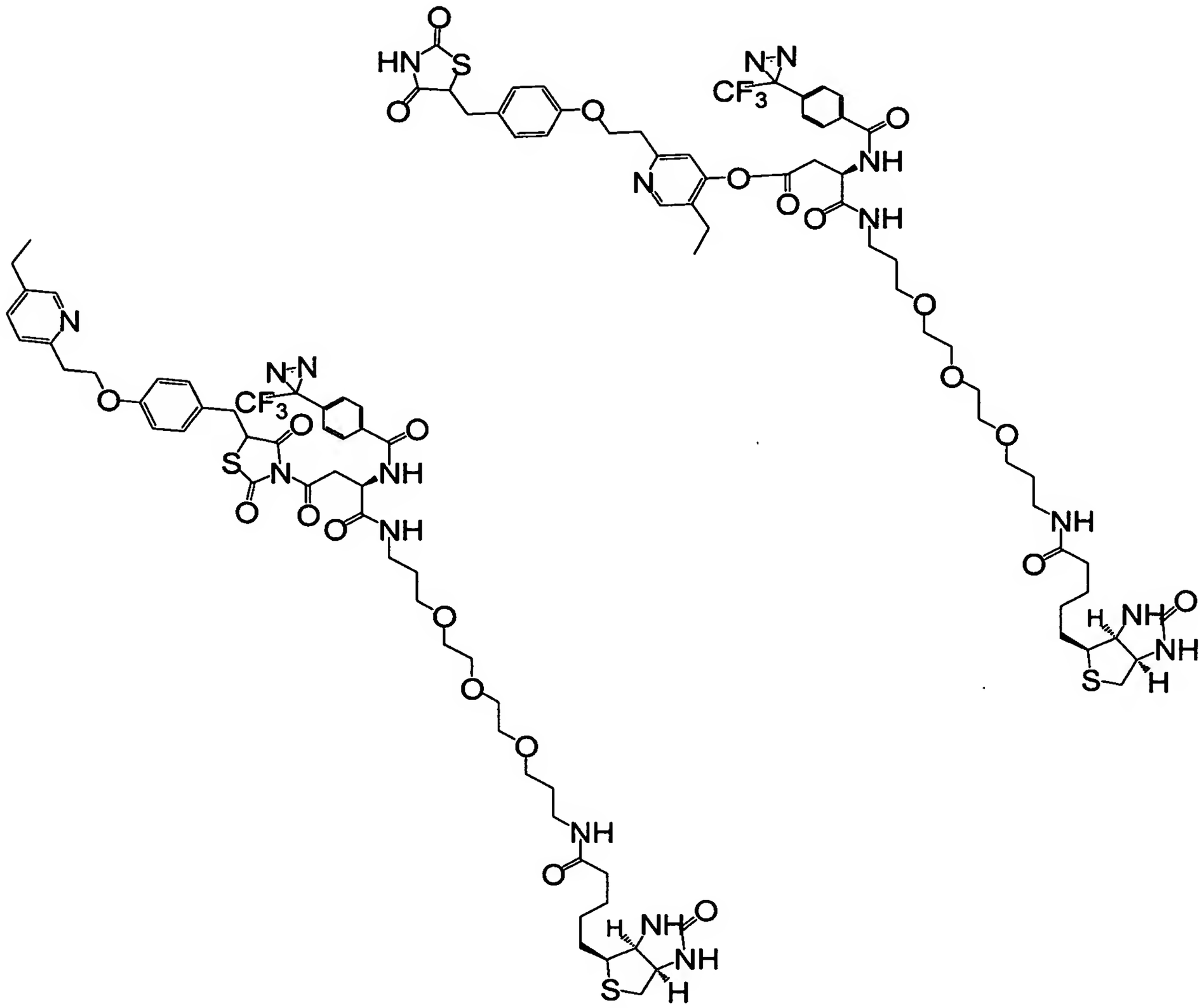


Metabolite

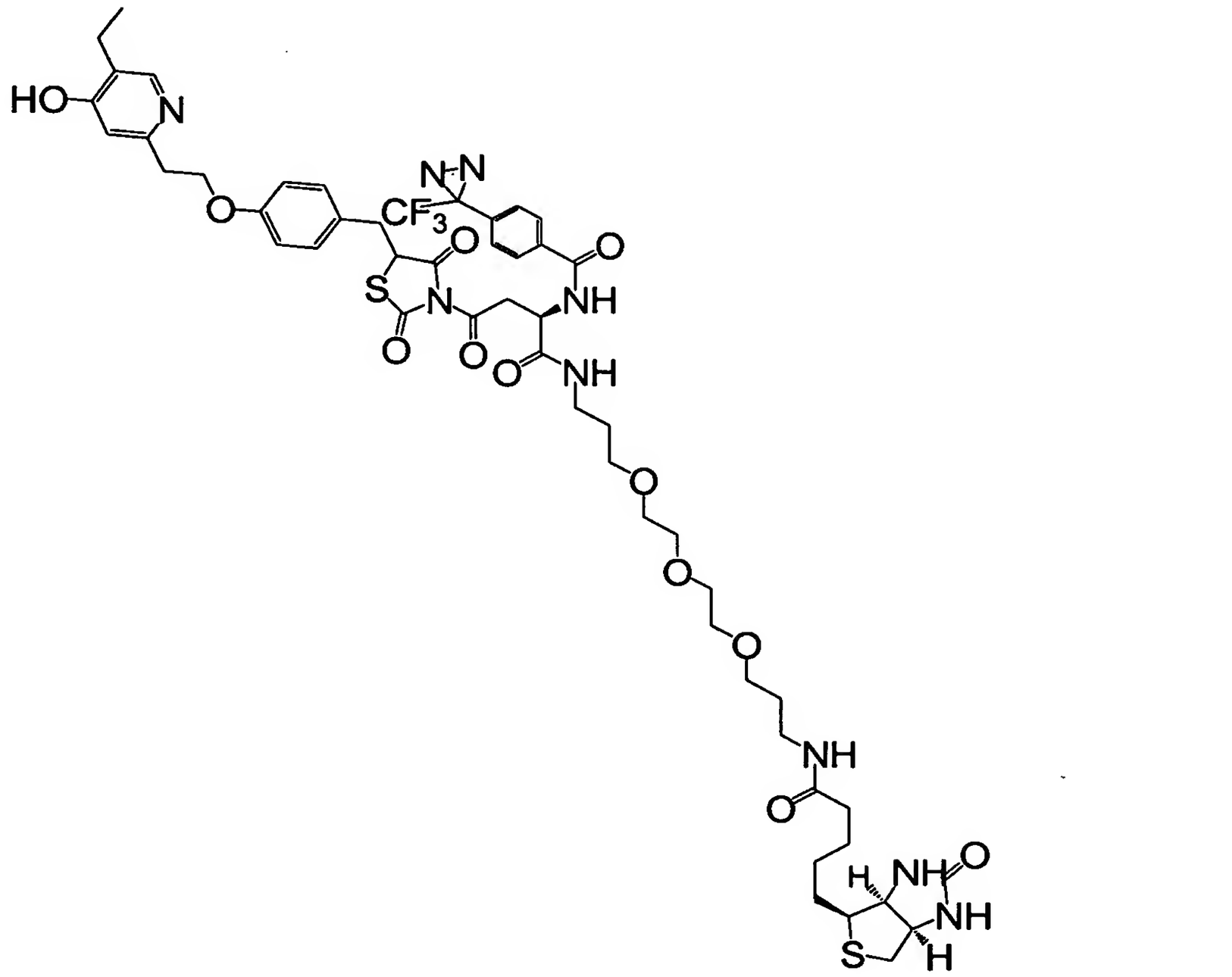
The capture compounds with Avandia and its metabolites attached to the Capture Compound are incubated with kidney, liver, pancreatic, colon epithelium, and muscle cells. The target protein PPAR-γ as well as non-target protein PPAR-α and protein A, B and C are captured.

Actos and Its Metabolites:

Actos is attached to the Capture Compound as depicted below:



Actos' metabolite is attached to the capture compound as depicted below:



Actos and its metabolites attached to the Capture Compound are incubated with kidney, liver, pancreatic, colon epithelium, and muscle cells. The target protein PPAR-γ as well as non-target protein PPAR-α and protein A, B and C are captured.

Thus, there is detailed description in the application, the original claims, description in the Examples, including Examples 14 and 16, and the depiction in Figure 30 and data in Figures 31-38 for practice of method as claimed. . Example 14 and Figures 31-38 describe and show practice of steps of the method. Disclosure in the specification describes the method and provides exemplary capture compounds that present a variety of drugs. The specification details exemplary Z, X, Y and Q moieties, including the extensive description in the specification and Figures 16 and 17. Example 16 explains in great detail how an exemplary family of drugs can be studied using the method. Example 16 shows the structure of capture compounds used in the method and also identifies metabolites and capture compounds containing metabolites. The Example identifies cells from which extracts and be prepared and incubated with the capture compounds, as in Figures 33-38. The captured products can be detected as in Figures 33-38. The application teaches and demonstrates how to practice the method as claimed and shows that capture compounds prepared as described

can be used to capture molecules that interact with a Y moiety that is user selected, such as a drug or drug metabolite or drug fragment.

e. Predictability in the art and the amount of experimentation

Predictability in the art refers to reproducibility of the claimed subject matter. There is nothing of record to suggest that the methods are not reproducible. The methods involve the use of compounds of a defined structure, whose components are well known in the art. As discussed above, many examples exist of capture compounds that present X moieties for capturing biomolecules. Each step in the method can be practiced without resort to further experimentation. The Y groups are user selected. Regarding predictability, Lauf *et al.*, relied on by the Examiner is not relevant to the instantly claimed methods. There is no need to discover and test new compounds. If necessary, capture compounds that present X groups are known and taught in the application and the Y groups are user selected. There is no need to explore the universe of compounds, but only to prepare compounds as described in the application for any particular drug studied.

The chemistry needed to prepare the compounds, while exemplified in the application, is based on textbook principles that go back years. No new synthetic methods are required.

As noted the specification details how to prepare compounds and lists exemplary X, Z and Q substituents. For the claimed embodiments , Y is a drug, drug fragment, drug metabolite or prodrug. The application provides numerous examples, and, clearly, such drug, drug fragment, drug metabolite or prodrug is user selected and can be linked to a Z core for presentation.

Conclusions

In light of the scope of the claims, the extensive teachings and exemplification in the specification, the high level of skill of those in this art, the working examples, and the extensive knowledge of those of skill in this art, the reproducibility of binding/capture methods, it would not require undue experimentation for a person skilled in the art to practice the methods as claimed. Accordingly, Applicant respectfully submits that full scope of all pending the claims is enabled.

Fairness

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

In this instance, applicant has disclosed and taught a generic method of identifying biomolecules that interact with a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug. It is unfair and unduly limiting to require applicants to limit the claims, when the application clearly teaches how to practice the method as claimed. Once one of skill in the art reads the specification, such person will be able to readily prepare and use any capture compound to identify biomolecules (drug targets and non-targets) that interact with a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug. The specification clearly places those of skill in the art in possession of a larger genus and teaches how to make and use such genus. To limit the claims to a few species as suggested by the Examiner, is unfair and contrary to the public policy upon which the U.S. patent laws are based. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304. If applicant is required to limit the claims to particular moieties X, Y, Z and Q, then those of skill in the art, by virtue of the teachings of this application, readily can use other moieties X, Y, Z and Q in capture compounds and practice the methods as disclosed in the application, but avoid infringement of claims so-limited. Clearly, the instant application, which teaches how to prepare capture compounds can be used to isolate and identify drug targets/non-targets that interact with a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug, teaches a generic method for doing so. Having done so, the application places the public in possession of such knowledge. Having provided this disclosure, others benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. Small early stage innovative companies can ill-afford to dedicate their innovations to the public.

Rebuttal to arguments of the Examiner:

1. The Examiner urges that:

> Applicant's claims are directed to a broad genus of methods for isolating and identifying biomolecules that have been "captured" by a capture compound *of* formula Q-Z-$(Y/X)_{n/m}$. The Q moiety is described as a sorting function, Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug. X is a ligand to a biomolecule that binds with sufficiently high affinity so that it will be "stable" under mass spectrometric analysis. And Z is moiety for presenting X, Y and Q. Thus, the claims encompass virtually an infinite number of methods employing virtually an infinite number of capture compounds because no structural limitations have been set forth. That is, Applicants have not limited the number of atoms, types of atoms, or the manner is way said atoms can be connected in defining the Q, X. Y and Z moieties. They could be composed of any element in the periodic table. Furthermore, the dependent claims also fail to limit at least one of the X, Y, Z, and Q moieties to anything less than an infinite number of possibilities. Thus, Applicant's claims encompass the entire universe of drugs, drug fragments, drug metabolites, sorting functions, ligands, etc. without exception. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

Applicant respectfully disagrees. As discussed above, in great detail, the claims are directed to a method comprising contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules in the sample. The claims recite that Z is a core for presenting X, Y, Z and Q. The application provides detailed description of Z moieties that can be used. X, the capture moiety is selected to, upon activation, covalently bind to biomolecules, and Q is a sorting function for immobilizing the capture compounds. The specification provides detailed guidance and exemplification of X and Q moieties. In addition, such moieties are well known to those of skill in the art. Y is drug, drug fragment, drug intermediate, drug metabolite or prodrug. Drugs, drug fragments, drug intermediates, drug metabolites and prodrugs are well-known to those of skill in the art. Selection of a Y is a user's choice, since the method is designed to identify molecules with which Y interacts.

The instant application provides the description and teaching for identifying biomolecules that interact with a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug by contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules. The application describes exemplary ways to identify a drug target (see, e.g. Figures, 20b-e and 33-38; Examples 10 and 14 and pages 151-155 of the application).

2 The Examiner urges that:

> . . .the predictability in the art is low when the full scope of the claims is taken into

> consideration. For example, Lauf *et al.* state, "The preparation of new materials with novel and useful chemical and/or physical properties is at best unpredictable considering current levels of understanding. Consequently, the discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Given approximately 100 elements in the periodic table, which can be used to make compositions consisting of three, four, five, six or more elements, the universe of possible new compounds remains largely unexplored." (e.g., see U.S. Patent Application Pub, No. 2004/0062911 Al, page I, paragraph 4). Thus, the presently claimed compounds by analogy "remain largely unexplored" because they could be constructed of any conceivable combination of elements in the periodic table. Furthermore, although organic chemistry (i.e., compounds restricted to a limited number of elements in the periodic table) is a mature art, it is not sufficiently developed to permit the synthesis of any pharmaceutical drug, drug fragment, drug intermediate, drug metabolite. etc. For example, Keaslin (sic) *et al.* state, "many natural products which would include pharmaceutical drugs, drug fragments, drug intermediates, drug metabolites, etc.) have complex structures, and, as a result, are currently ... impossible to synthesize- (e.g.. see Keasling *et al.*, US Patent Application No. 2006079476, paragraph 6).

Te claims are directed to methods for identifying targets/non-targets. The methods are not of an infinite nature, but require specified steps. The issue is not whether all possible compounds and drugs are taught in the application or whether all possible combinations of substituents could be synthesized, but whether one of skill in the art, in view of the specification and the other "Wands" factors can practice the method as claimed for a particular drug fragment, drug intermediate, drug metabolite or prodrug of interest. As discussed extensively above, the specification details and exemplifies how to make and use capture compounds and how to practice each step of the method. moiety for presenting X, Y and Q. There is no reason to doubt that one of skill in the art could identify targets/non-targets for particular a drug, fragment, metabolite, intermediate or prodrug thereof.

The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim .... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

THE REJECTION OF CLAIMS 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139. 140, 144, 150, 151, 152, 157. 158, 159, 160, 161, 163, 164, 166, 169 and 173 UNDER

35 U.S.C. §112, FIRST PARAGRAPH- WRITTEN DESCRIPTION

Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139. 140, 144, 150, 151, 152, 157. 158, 159, 160, 161, 163, 164, 166, 169 and 173 are rejected under 35 U. S. C. §112, first paragraph, as failing to comply with the written description requirement because the claim(s) allegedly contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner urges that the claims are directed to a broad genus of methods for isolating and identifying biomolecules that have been "captured" by a capture compound of formula Q-Z-(Y/X)n/m. The Examiner alleges that the specification does not define these moieties so that the "claims encompass the entire universe of drugs, drug fragments, drug metabolites, sorting functions, ligands, etc." The Examiner states that "the method employs molecules with Q, Z. X and Y that can only be distinguished from other compounds by their function." Furthermore, the Examiner urges that the knowledge and level of skill in the art do not supplement the omitted description because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the enormous genus. This rejection is respectfully traversed.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

The Federal Circuit has discussed the application of the written description requirement of the first paragraph of 112 to claims in the field of biotechnology. See University of California v. Eli and Co., 1 19 1559, 43 1398, 1406 (Fed. Cir. 1997). The court explained that:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . a generic statement such as "vertebrate insulin or "mammalian insulin without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by

> function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also stated that "[a]written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]chemical name, 'of the claimed subject matter sufficient to distinguish it from other materials." at 1567, 43 at 1405. Finally, the court addressed the manner by which a genus of might be described. "A description of a genus of may be achieved by means of a recitation of a representative number of species defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The written description for a claimed genus can be satisfied by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; see University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard.

The Federal Circuit also has addressed the written description requirement in the context of biotechnology-related subject matter in Enzo Biochem. Inc. v. Gen-Probe 296 1316, 63 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that:

> the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' [Emphasis added] at 3.

The court in Enzo adopted its standard from the Written Description Examination Guidelines. 296 at 1324, 63 at 3 (citing the Patent Office's own Guidelines). The Guidelines apply to proteins as well as nucleic acid molecules.

The written description requirement under 35 U.S.C. §112, is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.,* whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a parent application a device that inherently performs a function or

has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

Rejected claims

The rejected claims are discussed above.

Analysis

First, to satisfy the written description requirement it is not necessary for the application describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that an applicant invented the claimed subject matter. Thus, the fact that the specification does not describe or list all species within the scope of the claim not dispositive of the written description issue. The Enzo court stated that "the written description requirement can be met by that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 'at 63 at 3 (emphasis omitted, bracketed material in original).

To satisfy the written description requirement it is not necessary for the application describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that an applicant invented the claimed subject matter. Thus, whether or not the specification describes countless capture compounds is **not** dispositive. The Enzo court stated that "the written description requirement can be met by that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 'at 63 at 3 (emphasis omitted, bracketed material in original).

In this instance, the claims are directed to methods, **not to compounds.** The method as claimed is a generic method that can employs reagents known in the art. The method employs capture compounds to present a molecule of interest, in this case a drug, drug fragment, drug intermediate or metabolite or prodrug, on a capture compound that includes a group for capturing biomolecules. As discussed and established above, capture compounds

that present moieties for capturing biomolecules are well known; hence "Z" moieties and X moieties. Further, Q moieties, such as biotin and oligonucleotides, for immobilizing compounds on solid supports are well known to those of skill in the art. Furthermore, as discussed above, the application details selections for each moiety and exemplifies preparation of capture compounds and provides working examples.

The instant methods, which are new to the art, employ such compounds to present a moiety of interest, Y, such as a drug, drug fragment, drug intermediate or metabolite or prodrug, which is user selected. The method recites the steps of contacting the capture compound that presents the Y moiety with a sample, and allowing it to come to equilibrium and then activating X to capture any biomolecules that interact with Y. This is simple textbook chemistry using compounds and moieties that are known. As described and excerpted in detail above, the application describes the methods in great detail, including provision of "detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics" of the capture compounds that can be used in the methods.

Furthermore, the application details how to prepare and test compounds for the requisite activities. If needed, one of skill in the art, could prepare and test particular capture compounds for use in the method, just as Applicant describes for the exemplified compounds.

Therefore, the combination of the disclosure of the generic structure of capture compounds, lists of exemplary X, Z and Q moieties, the fact that capture compounds with such moieties are known in the art (see, e.g., Hutchens *et al.* (WO 98/59360), Cravatt *et al.* (WO 01/77668 and WO 01/77684), and Coull *et al.* (EP 0424 819), which are of record in this application), the working examples and generic description of practice of the claimed method, the high level of skill in the art, and the routine nature of the chemistry required demonstrates that Applicant sufficiently described and was in possession of the method as claimed as of the filing date and priority date of the application.

THE REJECTION OF CLAIMS 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116. 137, 139, 140. 144, 150, 151. 152, 157, 158, 159, 160, 163, 164, 166, 169 and 173 UNDER 35 U.S.C. §102(b)

Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116. 137, 139, 140. 144, 150, 151. 152, 157, 158. 159, 160, 163, 164, 166, 169 and 173 are rejected under 35 U.S.C.§ 102(b) as being anticipated by Hasegawa *et al.* (Biol. Chem. 1999, 27-1,44, 31713-31719) as evidenced by, Saeed *et al.*, Samanta *et al.* Chao *et al.*, Savige *et al.* and Kahne *et al.*

The Examiner states that Hasegawa *et al.*, allegedly discloses a method for the determination of the binding site on the extracellular domain of guanylyl cyclase c to a heat-stable enterotoxin by contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules in the sample. The Examiner urges that the capture compound, an STa analog, which is shown schematically in figure 1 B, allegedly contains a Z core that presents, Q, X and Y. The Examiner urges that the sorting function is Q is biotin-(AC5)2- Gly-Cys-Cys-G1u-Leu-Cys-Cys-; X = phenyl azide (i.e., a group that is selected to covalently bind to biomolecules) with n = 1; Y is Pro-Ala-Cys-Ala-Gly-Cys; Z = NH-$CH(CH_2)$-CO of the Pap group. The Examiner states that Hasegawa *et al.* discloses contacting the capture compound and the biomolecules for a sufficient time for the interaction reach equilibrium, followed by activation of "X" to capture the guanyl cyclase. The Examiner says that Hasegawa *et al.*. does not "state that the Pro-Ala-Cys-Ala-Gly-Cys segment is a drug or drug fragment" but relies on supporting references to allegedly show that this sequence is part of the STa enterotoxin (e.g., see Figure 1), which, secondary references allegedly demonstrate is a drug. The Examiner further contends that molecules that bind to this "drug" are identified and isolated:

> "Hasegawa *et al.* disclose (c) isolating and identifying the captured biomolecules to thereby identify biomolecules that interact with moiety Y (e.g., see Experimental; see also figures 3 and 4 identifying the isolated SPTFIWK sequence).

This rejection respectfully is traversed.

Relevant Law

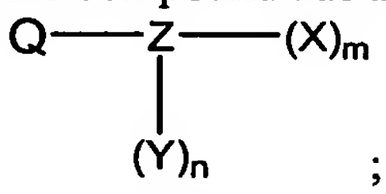
Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed subject matter is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

When a claimed invention is not identically disclosed in a reference, but requires picking and choosing from among a number of different options disclosed in the reference,

the **reference does not anticipate**. In re Arkley,, Eardly, and Long, 455 F.2d 586, 172 USPQ 524, 526 (CCPA) 1972). Picking and choosing is improper. Rejections under 35 U.S.C. §102 only are proper when a reference clearly and unequivocally discloses the claimed subject matter or directs those skill in the art thereto without any need for picking, choosing and combining various disclosures in the reference. See In re Le Grice, 49 CCPA 1124, 301 F.2d 9333. To anticipate the reference must place the public in possession of the claimed subject matter.

Rejected claims

Independent claim 1 is directed to a method for identifying targets and non-targets of a drug, drug fragment, drug intermediate, drug metabolite or prodrug; that includes the steps of:

> (a) contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules in the sample, wherein:
>
> the capture compound has the formula:
>
> 
>
> ;
>
> X is selected to covalently bind to biomolecules and requires activation following contacting with the biomolecules to effect covalent binding of the capture compound to a biomolecule;
>
> Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug;
>
> Q is a sorting function;
>
> Z is a moiety for presenting X, Y and Q;
>
> m is an integer that is 1 to 100;
>
> n is an integer from 1 to 100; and
>
> contacting is effected for a sufficient time for interaction between the capture compounds and the biomolecules to reach equilibrium;
>
> (b) activating X to form a covalent linkage or high affinity bond between X and biomolecule(s) in the sample that interact with Y to effect capture thereof; and
>
> (c) isolating and identifying the captured biomolecules, wherein the captured biomolecules comprise drug targets and non-targets.

Dependent claims recite particulars of the method, including particular capture compounds and additional steps.

Analysis

Hasegawa *et al.*

Hasegawa *et al.* is directed to a study designed to identify the STa (heat stable enterotoxin) binding region on the extracellular domain of guanylyl cyclase. Hasegawa *et al.* discloses use of a photoaffinity labeled analog of heat-stable enterotoxin: Biotinyl-$(AC_5)_2$-

[Gly^4,Pap^{11}]STp(4-17). (STp (4-17) is porcine STa with amino acids 4-17.) It is an analog of STp because it incorporates Pap moiety (*p*-azidophenylalanine) at position 11 and a biotin moiety at the N-terminus. This ligand is reacted with the extracellular domain of guanyl cyclase to indentify **the region of the extracellular domain of guanyl cyclase to which** the ligand STp binds. After covalently binding this ligand analog to the guanyl cyclase extracellular domain, the resulting complex is digested with Lys-C and the labeled residues identified by mass spectrometric analysis.

Differences between the disclosure of Hasegawa *et al.* and the instant claims

1) Biotinyl-(AC5)2-[Gly4,Pap11]STp(4-17) does not have the structure of the capture compounds used in the instantly claimed method.. The biotinyl-(AC5)2-Gly^4,Pap^{11}]STp(4-17) is an analog of residues 4-17 of STa and substitutes a p-azidophenylalanine at position 11. Not only is Pro-Ala-Cys-Ala-Gly-Cys (residues 12-17) part of the alleged "drug or drug fragment" because they are "part of the STa enterotoxin", the portion of the molecule corresponding residues 4-10 of biotinyl-(AC5)2-Gly^4,Pap^{11}]STp(4-17) are also the alleged "drug or drug fragment" because they are also part of the STa enterotoxin analog. Furthermore, six Cys residues are intramolecularly linked by disulfide linkages between Cys^5 and Cys^{10}, Cys^6 and Cys^{14}, and Cys^9 and Cys^{17} (see, e.g. Figure 1, caption), and the residues on both sides of position 11 are linked. Therefore, by the Examiner's definition, the "drug or drug fragment" includes residues on both the N- and C-terminal sides of the photoaffinity capture residue at position 11. Hence there is no portion of this molecule that corresponds to "Z" in the capture compounds of formula (I). Since the Examiner alleges that Q includes biotin, Hasegawa *et al.* does not disclose a method comprising a capture compound where Z is a moiety for presenting X, Y and Q as claimed in claim 1.

2) Notwithstanding 1), Hasegawa *et al.* does not disclose a method for identifying drug targets and non-targets in a sample by reacting the sample with a capture compound. Hasegawa *et al.* is probing a receptor to identify the residues on the receptor to which a particular ligand binds. Hasegawa *et al.* is not probing a sample to identify drug targets and drug non-targets. In the method of Hasegawa *et al.*, the target (receptor for the ligand) is known and provided. It is captured and then the portion of the receptor that interacts with the ligand analog is identified.

Thus, Hasegawa *et al.* fails to disclose a method that includes a step of identify drug targets and non-targets. Hasegawa *et al.* discloses a probe for photoaffinity labeling a

predetermined protein: the extracellular domain of Guanylyl Cyclase C (ECD6H). Hasegawa *et al.* prepared biotinyl-(AC5)2-Gly^{4},Pap^{11}]STp(4-17) for photoaffinity labeling of ECD6H" (see, e.g. page 31715, left column, last full paragraph of Hasegawa *et al*). Even assuming that enterotoxin is a drug (which Applicant **does not** concede), Hasegawa *et al.* does not disclose a method in that identifies molecules with which a drug, drug fragment, drug metabolite, drug intermediate or prodrug interact. The captured molecule in the experiment of Hasegawa *et al.* is **known; it is not identified**. In contrast, in the instantly claimed method, the molecules with which a capture compound that presents a drug, drug fragment, drug metabolite, drug intermediate or prodrug interacts <u>are **identified by the method**</u>. Therefore, Hasegawa *et al.* does not disclose a method of **identifying** biomolecules (drug targets/non-targets) that interact with a drug, drug fragment, drug intermediate, drug metabolite or prodrug. Therefore, Hasegawa *et al.*, does not disclose all elements as claimed and does not anticipate claim 1, nor any claim dependent thereon.

THE REJECTION OF CLAIMS 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160, 161, 163, 164, 166, 169 and 173 UNDER 35 U.S.C. §103(a)

Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160, 161, 163, 164, 166, 169 and 173 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hasegawa *et al.* I in view of Hasegawa *et al.* II as evidenced by, if necessary, Saeed *et al.* (WO 2006/138571 A2, which is **Not** prior art, and Samanta *et al.* and Chao *et al.* and Kahne *et al.* The Examiner urges that Hasegawa *et al.* teaches all of the limitations of claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 150, 151, 152, 157, 158, 159, 160, 163, 164, 166, 169 and 173, but for claim 161, Hasegawa *et al.* fails to teach a method for disclose a method for determining a dissociation constant. Hasegawa *et al.* only determined I_{50} values (e.g., see page 3 I 715, column 1, paragraph 2), but this deficiency is provided by Hasegawa *et al*, II, which teaches "the use of calculating $K_{D)}$ values to compare in a quantitative fashion the binding affinity of similar peptides (e.g., see abstract; see also Materials and Methods; see also Results)." The Examiner concludes that :

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to calculate the $K_{D)}$ value of the biotinyl-(AC5)2- [Gly^{4},Pap^{11}]STp(4-17) molecule as disclosed by Hasegawa *et al.* using the method as disclosed by Hasegawa *et al.* II because K_D values were commonly employed as a tool for characterizing the binding affinity of ligand for a protein target (e.g., see Hasegawa *et al.* II, abstract). A person of ordinary skill in the art would have been motivated to

> calculate the K_D) because it offers an easy, quantitative method for comparing binding affinities that is universally employed in the field of chemistry/biochemistry. A person of ordinary skill in the art would have reasonably expected to be successful because Hasegawa *et al.* II shows that K_D) values can be calculated for nearly identical peptides toxins against the same GC-C targets (e.g., see abstract; see also Materials and methods).

This rejection is respectfully traversed.

Relevant Law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103(a), there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-Fabrik GMBH v. American hoist and Derrick co., 730 f.2d 1452, 1462, 221 u.s.p.q.2d 481, 488 (fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 u.s.p.q.2d 1780 (Fed. Cir. 1992); see, also, in re Papesch, 315 f.2d 381, 137 u.s.p.q. 43 (ccpa 1963). In addition, if the proposed modification or combination of the prior art would change the principle of

operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 f.2d 810, 123 uspq 349 (ccpa 1959).

For *prima facie* obviousness of a claimed subject matter to be established, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This bedrock principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit some reason that would have led a person having ordinary skill in the art to modify a known composition in a particular manner and thereby result in the claimed composition. Absent such a reason, the claimed composition would not have been obvious.

The rejected claims

Differences between the teachings of Hasegawa *et al.* and the instant claims

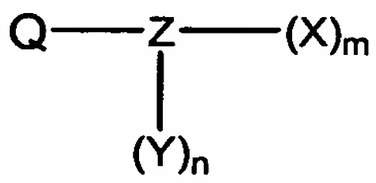
Hasegawa *et al.* is discussed above. As discussed above, it is directed to a study designed to identify the STa (heat stable enterotoxin) binding region on the extracellular domain (ECD) of guanylyl cyclase. To identify this region, Hasegawa *et al.* employs a photoaffinity labeled analog of heat-stable enterotoxin. The analog incorporates a Pap moiety (*p*-azidophenylalanine) at position 11 in the STa analog and a biotin moiety at the N-terminus. This ligand is reacted with the extracellular domain of guanyl cyclase and the resulting labeled guanyl cyclase ECD is isolated and digested. The labeled fragment is identified by mass spectrometry to thereby identify the amino acid residues in guanyl cyclase the bind to the enterotoxin.

As discussed above, the photoaffinity labeled analog does not meet the definition of a capture compound (even if one would accept (and Applicant does not) that enterotoxin is a drug) because the Pap moiety is in the middle of the drug inserted at residue 11. Hence, there is no Z that presents an X, Y and Q.

Notwithstanding such failure, Hasegawa *et al.*, fails to teach, suggest or even hint at a method for identifying drug targets/non-targets. Hasegawa *et al.* is directed to a method for identifying the residues in the enzyme to which enterotoxin binds. This is completely and unequivocally different from a method that the identifies drug targets and non-targets with which a particular drug interacts. There is no suggestion of such method in

Hasegawa *et al.* One of ordinary skill in the art, in view of Hasegawa *et al.*, alone or in combination with the secondary references, would not have been led to a method for identifying method for identifying targets and non-targets of a drug by:

> (a) contacting a capture compound that presents a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug with a sample containing biomolecules for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium;
>
> (b) activating X to form a covalent linkage or high affinity bond between X and biomolecule(s) in the sample that interact with Y to effect capture thereof; and
>
> **(c) isolating and identifying the captured biomolecules, wherein the captured biomolecules comprise drug targets and non-targets.**
>
> The capture compounds are of formula:



in which

> Z is a moiety for presenting X, Y and Q;
>
> X is selected to covalently bind to biomolecules and requires activation following contacting with the biomolecules to effect covalent binding of the capture compound to a biomolecule;
>
> Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug;
>
> Q is a sorting function;
>
> m is an integer that is 1 to 100; and
>
> n is an integer from 1 to 100.

As discussed above, not only does not Hasegawa *et al.* not teach a compound of the requisite formula, it does not teach a method that includes a step of identifying drug targets and targets. In the study in Hasegawa *et al.*, an analog of a ligand was used to affinity label its receptor in order to identify the residues in the receptor to which the ligand binds. There is no suggestion in Hasegawa *et al.*, nor any other reference of record, to modify the method for identifying molecules with which a drug, drug fragment, drug intermediate, drug metabolite or prodrug interact. There certainly is no suggestion for doing so in order to thereby assess drug interactions for redesign or to identify causes of side-effects.

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, in re Papesch, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In this instance, there is no suggestion in the cited art for any modification of the study of Hasegawa *et al.* nor any suggestion that would have led one of ordinary skill in the art to the instantly claimed methods.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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